# HIGH ARTERIAL PRESSURE

# HIGH ARTERIAL PRESSURE

F. H. SMIRK
M.D., F.R.C.P., F.R.A.C.P.
*Professor of Medicine University of Otago*
*Dunedin - New Zealand.*

BLACKWELL
SCIENTIFIC PUBLICATION
OXFORD

*Published simultaneously in the United States of America by Charles C Thomas, Publishers, 301/327 East Lawrence Avenue, Springfield, Illinois.*

*Published simultaneously in Canada by the Ryerson Press, Queen Street West, Toronto, 2.*

First printed, October 1957.

Printed in Holland for BLACKWELL SCIENTIFIC PUBLICATIONS, LTD
by the late HOITSEMA BROTHERS, Groningen
and bound at the KEMP HALL BINDERY, Oxford.

For
AILEEN
AND TO THE MEMORY OF
MY PARENTS

## Preface

The author wishes to express his indebtedness to all those who have given help in the preparation of this book.

The competent and accurate secretarial work of Miss N. Richardson Miss P O'Callaghan, Miss J. Fitzgerald and at an earlier stage of Mrs M. Fleury, is acknowledged with gratitude. The original diagrams were mostly drawn by Miss W. Thornton. The photography was undertaken by the Medical School photographic department and Mr K. J. White did much work in his own time, Mrs. D. Lemon did the photomicrography and Mr G Brook provided many of the photographs used. The histology was undertaken by Miss R. Galway, and I am indebted to our pathology department for providing the blocks. I am grateful to our laboratory staff, to the technicians of the hypertensive clinic, to the library staff and to senior members of the nursing staff for their unfailing help.

Doctors E. G. McQueen, A. M. O. Veale, M. Hamilton, T. V. O'Donnell, J. A Kilpatrick, R. O H Irvine, D. R. Hay, L. W. Field, and Mr R. Laverty have kindly allowed reference to be made to unpublished work Sir Charles Hercus, Dr. A. E. Doyle, Dr. F. N. Fastier, Dr. W Ironside, Dr. G. Blake Palmer, Mr. L. W. Cox and Dr. Roland P. Wilson have kindly read over various chapters. Dr. E. G. McQueen and Dr. F N Fastier have been particularly helpful I am indebted to many physicians for their consideration in referring hypertensive patients to me. My thanks are due to house physicians, registrars and more senior colleagues whose cooperation and thoughtfulness made possible some spare time for writing.

The author is grateful for permission to reproduce figures and tables and for permission to quote from published papers. Permission to use Dr. M. Rosenheim's coloured illustrations of the retina was particularly welcome Reference to the authors and publishers is made in the text.

The work in this field of hypertension, coming from the department of which the author is a member, could not have been undertaken without financial support and other facilities. Grateful acknowledgement for these is made to the Council of the University of Otago, the New Zealand Medical Research Council, the Life Insurance Medical Research Fund of Australia and New Zealand, and the Otago Hospital Board.

lian colleagues. A Rockefeller Grant in 1954 enabled the author to attend the International Congress of Cardiology in Washington, U.S.A., and an invitation from the Wellcome Foundation in 1956 to attend a conference in London on hypotensive drugs made it possible to have discussions with many colleagues who share an interest in this subject. I am most grateful to the trustees of these foundations. The helpful cooperation of the publishers, particularly their late acceptance of manuscript relating to recent publications, is gratefully remembered.

I hope inadvertent failure to acknowledge adequately the work of others has been infrequent. Deficiencies, though regretted by the author, are inescapable when there is a great volume of literature, and indeed it has not been practicable to refer to all the interesting and valuable work on the subject.

For continued encouragement and help the author is beholden to his wife.

## CONTENTS

CHAPTER IV

INFLUENCE OF CHANGES IN LIVING CONDITIONS ON THE BLOOD PRESSURE LEVEL

Page



## Chapter V

## THE CLINICAL MANIFESTATIONS OF HYPERTENSION

Page

## Chapter VI
## AETIOLOGY

188

## CHAPTER VII

## PSYCHOSOMATIC ASPECTS OF HIGH BLOOD PRESSURE

CHAPTER VII

## PSYCHOSOMATIC ASPECTS OF HIGH BLOOD PRESSURE

Chapter VIII

## THE PHYSIOLOGY OF BLOOD PRESSURE REGULATION

## CHAPTER IX
## EXPERIMENTAL HYPERTENSION

CHAPTER XII

PROGNOSIS OF HYPERTENSION
(in the absence of definitive treatment)

Page

Chapter XIII

## SOME FUNDAMENTAL PRINCIPLES CONCERNING THE TREATMENT OF HYPERTENSION BY BLOOD PRESSURE REDUCTION



Chapter XIV

## SURGICAL TREATMENT OF HIGH BLOOD PRESSURE

CHAPTER XII

## PROGNOSIS OF HYPERTENSION
**(in the absence of definitive treatment)**

## CHAPTER XV

## SEVERE SALT RESTRICTION



## CHAPTER XVI

## HYPOTENSIVE DRUGS, MOSTLY OF ACADEMIC INTEREST

Chapter XVII

## THE RAUWOLFIA ALKALOIDS

CHAPTER XVIII

## PHARMACOLOGY OF GANGLION BLOCKING DRUGS

## CHAPTER XVIII
## PHARMACOLOGY OF GANGLION BLOCKING DRUGS

## CHAPTER XIX

## TREATMENT OF PATIENTS BY GANGLION BLOCKING AGENTS

CHAPTER XIX

## TREATMENT OF PATIENTS BY GANGLION BLOCKING AGENTS

CHAPTER XIX

## TREATMENT OF PATIENTS BY GANGLION BLOCKING AGENTS

CHAPTER XX

## COMBINED THERAPY



CHAPTER XXI

## RESULTS OF TREATMENT

*"If I were bold enough to be a prophet, I should point to the time when the elder folks, instead of waiting till they have had a stroke of apoplexy or a touch of paralysis, or are laid up with arterio-capillary fibrosis or morbus Brightii, and then hurriedly summoning a physician to do impossibilities, will seek his advice betimes, asking him to supervise their vital functions, regulate their mode of life, and teach them to stay the morbid changes which they know may be silently progressing".*

Some experience of the Sphygmograph in Medicine.
C. Handfield Jones Lancet, 1878

CHAPTER I

## Introduction

The disorder hypertension is not only one of the most interesting but one of the most important subjects in the realm of medicine. Hypertension may lead ultimately to adverse manifestations in 30, perhaps in 40 per cent of persons born alive in communities with a high standard of living; and probably it plays some part in the final cause of death of between 20 and 30 per cent of the population. In the United States of America alone in 1949 there were 4,600,000 persons living who had received or were receiving medical attention for high blood pressure With diminished death rates it must be expected that the number will increase.

Hypertension, as Riseman said, is "not conducive to longevity but is compatible with longevity". It may reduce the expectation of life to a few months or may have no important effect upon life's duration. The disorder is so common and so well known by the lay public [illegible]

[illegible] some cases, and it is important that such cases should be recognized and that the patient should be fully reassured The most effective reassurance is based on facts which are true and can be told convincingly.

About 1936, in the course of some experiments with my former colleague, Dr Alam, it was noticed that in habituated [illegible]

[illegible] casual blood pressure for random measurements, "basal" blood pressure for the blood pressure under certain defined basal conditions, and "supplemental" blood pressure for the labile fraction of the blood pressure (casual minus basal).

This work prompted investigations which led me to think that essential hypertension is not due to a single pathological process: that

*"If I were bold enough to be a prophet, I should point to the time when the elder folks, instead of waiting till they have had a stroke of apoplexy or a touch of paralysis, or are laid up with arterio- capillary fibrosis or morbus Brightii, and then hurriedly summoning a physician to do impossibilities, will seek his advice betimes, asking him to supervise their vital functions, regulate their mode of life, and teach them to stay the morbid changes which they know may be silently progressing".*

Some experience of the Sphygmograph in Medicine
C Handfield Jones, Lancet, 1876.

CHAPTER I

## Introduction

The disorder hypertension is not only one of the most interesting but one of the most important subjects in the realm of medicine. Hypertension may lead ultimately to adverse manifestations in 30, perhaps in 40 per cent of persons born alive in communities with a

blood pressure With diminished death rates it must be expected that the number will increase.

Hypertension, as Riseman said, is "not conducive to longevity but is compatible with longevity". It may reduce the expectation of life to a few months or may have no important effect upon life's duration The disorder is so com

of hypertension is revealed. Yet the prognosis is definitely good in some cases, and it is important that such cases should be recognized and that the patient should be fully reassured The most effective reassurance is based on facts which are true and can be told convincingly.

About 1936, in the course of some experiments with my former colleague, Dr. Alam, it was noticed that in habituated normal subjects in an unstimulating environment, the blood pressure fell to surprisingly low levels. Out of this work came a study of the basal blood pressure and the use of the term "casual" blood pressure for random measurements, "basal" blood pressure for the blood pressure under certain defined basal conditions, and "supplemental" blood pressure for the labile fraction of the blood pressure (casual minus basal).

This work prompted investigations which led me to think that essential hypertension is not due to a single pathological process: that

it may begin in some cases with the simple overactivity of physiological processes, whereas in others pathological changes may be primary.

The invitation of my friend, Dr. John McMichael, to act as visiting professor at the British Postgraduate Medical School, Hammersmith, in 1948, and to speak on this subject, stimulated me to clarify my ideas, and finally to adopt the working hypothesis that essential hypertension is a disorder of function which is the resultant of the action of many physiological and pathological factors, which produce their clinical manifestations through the intermediation of blood pressure elevation. In essential hypertension the basic causes remain clinically inconspicuous, except in so far as they lead to a rise of blood pressure, and thence to secondary manifestations. Hence we may say that as the blood pressure rises we witness the emergence of essential hypertension as a recognizable disorder. It follows that to anyone holding this as a working hypothesis, the study of pathogenesis becomes an attempt to disentangle the component causes and study their interrelationships.

Sometimes the clinical manifestations and outcome of hypertension do not appear to be closely related to the level of the casual blood pressure; but this is not surprising. The measurement of the casual blood pressure in the doctor's office is only a sample blood pressure, and there is good evidence that in many patients it is not a representative sample. The basal blood pressure, however, is much less variable than the casual blood pressure; indeed in health it is a physiological constant for the individual It will be seen that the basal blood pressure may be measured by a simple technique suitable for general practice, and that it is probably the most important single ancillary investigation to be undertaken in patients with overaverage casual blood pressures. Our experience over a period of eight years with basal blood pressures, measured in about 1,000 patients, and a population survey, will be referred to. The clinical manifestations and the prognosis of hypertension will be found to be much more closely related to the basal than to the casual blood pressure and reference will be made also to its use in the selection of patients for drug therapy.

Several chapters have been devoted to pharmacology and to therapy. Although experimental pharmacology illuminates and is a necessary prelude to clinical pharmacology, the basis of drug therapy is clinical pharmacology. The physician must know what has been discovered in man. For this reason, separate but adjacent sections have been written on experimental and clinical pharmacology.

Drugs which the author does not recommend have been described in some detail for two reasons. First, that it is desirable to represent the views of those who have found such drugs helpful, and secondly, because the information about them forms a valuable background of knowledge which may aid the evaluation of new drugs.

Much space has been devoted to the details of treatment because I think success and the comfort of patients depends on these. The patient with severe hypertension has the prospect of a lifetime of treatment, hence the relief of even small recurring discomforts, the removal of restrictions which are unnecessary, and the promotion of confidence are important. The comfort of patients on hypotensive drugs depends largely on the application of a knowledge of pharmacology to the solution of their personal problems. The gains of therapy must not be counted only in the dispersal of retinal exudates and improvements in the electrocardiogram, but in the resumption of normal activities appropriate to the patient's age. This aim, however, [illegible]

formance of a surgical sympathectomy the failure to sterilize one instrument or to tie one blood vessel may prejudice the result of the procedure It is not so easy to appreciate that the same holds true for "medical sympathectomy". But, unfortunately, at the present time, it does.

Since January, 1950, our Dunedin Hospital hypertensive clinic has treated over 500 patients with various hypotensive drugs. The experience gained has made it possible to suggest ways in which the régimes of patients on such drugs can be made more efficient and comfortable We now feel confident that activity is restored for several years and that the duration of life is extended appreciably in certain hypertensive patient groups.

As most books on clinical subjects are used both for consecutive reading and for reference on problems arising in practice, I have preferred an arrangement in this book which I hope will make accessible the kind of information which is needed, sometimes urgently, in connection with particular problems.

It will be recognized that many subjects have a rightful place in several chapters. For example, in the chapter on aetiology much space is given to unusual disorders, such as aneurysm [illegible] which [illegible]
Such ch[illegible]
of hype[illegible] pathogenesis as well as the aetiology of hypertension.

Fortunately subjects such as pathogenesis are more likely to be studied by the reader at times when it is practicable to start at page one and [illegible]
at the ch[illegible] [illegible]ing
made in [illegible] are
subjects [illegible] involve reference to several chapters. [illegible] on

CHAPTER II

# CASUAL, BASAL AND SUPPLEMENTAL BLOOD PRESSURES

Curious about the facts of nature, the Reverend Stephen Hales in 1733 described the results of his experiments on the blood pressure of a mare. He introduced a tube into the left crural artery, and noted the pulsations as the blood mounted the tube. He also observed a slower periodic fluctuation which we know now as Traube-Hering waves.

It was Richard Bright, of Guy's Hospital, London, who first directed attention to the possibility that in renal disease there might be an increase in resistance to the flow of blood through the minute vessels of the body, and he implied that the cardiac hypertrophy which he had observed *might arise from this. These observations* were published mainly between 1827 and 1836.

The early observations of Bright seem to have had comparatively little immediate influence on the medical thought of the times. Approximately 100 years ago, half-yearly abstracts of the medical sciences were published, very much on the lines of our present year books. In the volumes of 1854, 1855 and 1856 I found no reference to the subject of blood pressure.

There existed at that time no means of measuring the blood pressure clinically and for a time pulse tracings were used as an indication of raised or lowered arterial tension.

## MEASUREMENT OF THE BLOOD PRESSURE

A variety of indirect methods for the measurement of blood pressure were devised between 1855 and *1896* [10, 17, 18, 19, 21, 24, 26, 27, 36, 37, 38], but active clinical interest in blood pressure measurement began with the introduction of the pneumatic cuff by Riva-Rocci in 1896; and, for many years, measurement of the blood pressure was regarded as a special research-type of investigation.

No attempt will be made to give an historical account of the methods used. Many of the early instruments have been described and illustrated by Master et al. (1952), as well as more modern instruments. An admirable description of other instruments can be found in "Blood Pressure: Its Clinical Applications" by Norris (1917). The methods used include mercury manometers, compressed air manometers, anaeroid manometers, spring manometers, various devices for graphic registration and oscillometers.

### Auscultatory Method

When a sphygmomanometer cuff around the upper arm is inflated to above the systolic blood pressure and is slowly deflated the following auscultatory changes may be heard:

(1) A faint clear sound which denotes the systolic pressure. The sound increases in intensity as the cuff pressure is lowered.

(2) A sound which acquires the character of a murmur.

(3) A sound of greater intensity, the murmur having disappeared.

(4) A muffled sound.

(5) Disappearance of the sound.

In 1939 a Committee of the American Heart Association and of the Cardiac Society of Great Britain and Ireland, recommended that the diastolic blood pressure should be taken when the sound becomes muffled. In 1951 the American Heart Association stated that the disappearance of sound was more closely related to the diastolic blood pressure as measured directly, but in some recent publications a preference is expressed for the 1939 pronouncement. The matter is not yet decided. As a rule the difference in pressure between the fourth and fifth phases (muffling and disappearance of sound) is usually of the order of 5 to 10 mm. Hg.

Accuracy in blood pressure measurement is aided by observing the following precautions:

(1) The cuff should be placed so that the rubber bag lies over the brachial artery.

(2) If the arm is of overaverage girth, 14 or 16 cm. wide cuffs may be used. If the standard cuff only is available, and if it tends to bulge when inflated, it should be held in place by wrapping 3 or 4 inch wide bandage on the outside.

(3) The arm should be supported at heart level.

(4) As one approaches the systolic and diastolic pressures deflation of the cuff should proceed *very slowly* — when deflation is rapid the mercury column registers a pressure which is lower than the cuff pressure.

(5) Record which arm is used for measurement; pressures are sometimes a little higher in the right arm.

(6) If a *definite diastolic* pressure end point is difficult to obtain: let the pressure out of the bag, elevate the arm for 5 or 10 seconds inflate the bag with the arm elevated [illegible] and [illegible] to induce vasodilatation [illegible] above manoeuvre.

The blood pressure usually decreases as measurements are repeated. It is useful to record the highest and lowest levels observed.

(7) Until it has been ascertained that there is no "auscultatory

gap" the cuff should be inflated to above 220 mm. Hg. The early literature on this subject is reviewed by Mudd and White (1928).

### Intra-Arterial Methods

Much attention has been given lately to the relationship between auscultatory blood pressure measurements and so-called direct readings obtained with an intra-arterial needle. Some authors think that, in general, the results of indirect measurements of the brachial blood pressure, using the standard 12 cm. *sphygmomanometer cuff* on arms of average girth, are close to those registered by electrical or optical devices to which the pressure is conveyed through an intra-arterial needle (Hamilton et al., 1936; Ragan and Bordley, 1941; Steele, 1941; Kotte et al., 1944).

Most authors have agreed that the systolic pressure is under-estimated by the indirect method. Van Bergen et al. (1954) state that, using the proper size of cuff and slow deflation, the auscultatory systolic pressure will be equal to or less than the intra-arterial pressure but will not exceed it. Roberts, Smiley and Manning (1953) found that auscultatory systolic pressure readings were, as an average, 4 mm. below strain gauge readings, and 12 mm. below electromanometer readings. It is clear from the figures of Van Bergen et al. (1954) that, as the blood pressure increases, the difference between the intra-arterial and cuff pressures also increases. This applies to both systolic and diastolic pressures.

The relationship between intra-arterial diastolic pressure readings and cuff pressures is complicated by the question of whether the diastolic pressure should be recorded at the time when the sound muffles (4th phase), or when the sound disappears (5th phase). Thus, Steele (1942), whose work was referred to in the American Heart Association report, stated that, in comparison with the intra-arterial method, the auscultatory method underestimates the systolic pressure by *10 mm., and the diastolic pressure (4th phase) by 8.8 mm.* The disappearance of sound (5th phase) seemed to Steele to give a closer correspondence with the intra-arterial pressure than muffling (4th phase). Roberts et al. (1953) and Van Bergen et al. (1954) however, considered that a better agreement between intra-arterial readings and auscultatory diastolic pressures is obtained at the 4th phase.

It is often assumed that when comparisons are made between cuff and intra-arterial readings that the intra-arterial readings may be taken as correct The intra-arterial readings used for comparison, however, are not mean pressures measured directly against a mercury column but are systolic and diastolic pressures which depend upon the registration of rapid changes of pressure by a strain gauge or other manometric device, and upon the properties of the

by the two transducers with which they are connected may be significantly different, as was shown by Roberts, Smiley and Manning (1953). Direct and indirect readings of the brachial artery pressure do not, in any case, represent [illegible] other major arterial tributaries. There seems no reason to doubt [illegible]

[illegible] much under the influence of the emotional state of the patient, that the error introduced by the exhibition of laboratory equipment and the procedure of brachial artery puncture, may be much bigger than that involved in the indirect procedure

The main objections to indirect measurement are those which arise from fat arms, and direct measurement may be worth-while in order to decide whether the blood pressure is high or not. The superiority of direct measurements for recording very rapid changes of blood pressure is generally recognized.

## Influence of Arm Girth on Blood Pressure Measurement

[illegible] pre[illegible] size [illegible] the results obtained by indirect measurement of the blood pressure are influenced by the width of the cuff employed for the purpose. Fishberg (1954) emphasizes the importance of a rigid cuff in obese patients, especially those with short arms. Otherwise the length of artery compressed will be too small.

An experiment has often been quoted in which the estimated blood pressure was compared in two unequally developed arms (Hensen, 1900, Janeway, 1903). The estimated blood pressures were found to be equal and it was concluded that the results were uninfluenced by arm girth. Hensen [illegible] results in only two patients — one ha[illegible] one patient. Some observations made he[illegible] tients with unequal arms showed slight [illegible] repetitions, the higher reading being [illegible] with the larger circumference. The average differences obtained in these 8 patients were 126 3/77 9 mm of mercury for an average arm girth of 10 inches and 119.1/78 2 for an average arm girth of 8 06 inches

If an arm is artificially thickened by wrapping around it various materials such as cloth, cotton wool, sponge rubber and meat from the butcher, it is found that these materials have different effects upon the estimated blood pressure. Cloth and meat of a rather compact consistency had very little effect upon the estimated blood pressure, whereas cotton wool and sponge rubber increased the estimated blood pressure. Apparently what happens is that some materials when interposed between the sphygmomanometer cuff and the artery spread the pressure over a wider area so that, in fact, the pressure

gap" the cuff should be inflated to above 220 mm. Hg. The early literature on this subject is reviewed by Mudd and White (1928).

### Intra-Arterial Methods

Much attention has been given lately to the relationship between auscultatory blood pressure measurements and so-called direct readings obtained with an intra-arterial needle. Some authors think that, in general, the results of indirect measurements of the brachial blood pressure, using the standard 12 cm. sphygmomanometer cuff on arms of average girth, are close to those registered by electrical or optical devices to which the pressure is conveyed through an intra-arterial needle (Hamilton et al., 1936; Ragan and Bordley, 1941; Steele, 1941; Kotte et al., 1944).

Most authors have agreed that the systolic pressure is underestimated by the indirect method. Van Bergen et al. (1954) state that, using the proper size of cuff and slow deflation, the auscultatory systolic pressure will be equal to or less than the intra-arterial pressure but will not exceed it. Roberts, Smiley and Manning (1953) found that auscultatory systolic pressure readings were, as an average, 4 mm. below strain gauge readings, and 12 mm. below electromanometer readings. It is clear from the figures of Van Bergen et al. (1954) that, as the blood pressure increases, the difference between the intra-arterial and cuff pressures also increases. This applies to both systolic and diastolic pressures.

The relationship between intra-arterial diastolic pressure readings and cuff pressures is complicated by the question of whether the diastolic pressure should be recorded at the time when the sound muffles (4th phase), or when the sound disappears (5th phase). Thus, Steele (1942), whose work was referred to in the American Heart Association report, stated that, in comparison with the intra-arterial method, the auscultatory method underestimates the systolic pressure by 10 mm., and the diastolic pressure (4th phase) by 8 8 mm. The disappearance of sound (5th phase) seemed to Steele to give a closer correspondence with the intra-arterial pressure than muffling (4th phase). Roberts et al. (1953) and Van Bergen et al. (1954) however, considered that a better agreement between intra-arterial readings and auscultatory diastolic pressures is obtained at the 4th phase.

It is often assumed that when comparisons are made between cuff and intra-arterial readings that the intra-arterial readings may be taken as correct The intra-arterial readings used for comparison, however, are not mean pressures measured directly against a mercury column but are systolic and diastolic pressures which depend upon the registration of rapid changes of pressure by a strain gauge or other manometric device, and upon the properties of the tubes transmitting the pressures It is possible that indirect measurements of the blood pressure by the cuff method may provide, *in certain circumstances*, a more faithful and representative reading of the blood pressure than pressures

EFFECT OF CUFF WIDTH

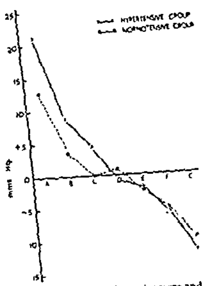



Fig. II 2

Effect of cuff width on sphygmomanometer measurements in hypertensives and normotensives.

*Ordinates* Represent sphygmomanometer readings using cuffs of various widths minus simultaneous sphygmoma- [illegible] degree of under-estimation of the blood pressure (compared with the standard cuff) is the same in hypertensives and normotensives. The rate of change of apparent blood pressure with change in cuff width is least with cuffs of 10 — 14 cm. widths.

EFFECT OF CUFF WIDTH

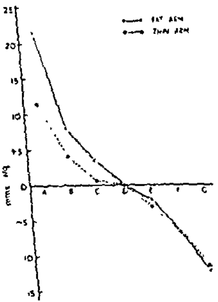



Fig. II 3

Effect of cuff width on sphygmomanometer measurements in fat and thin arms.

*Ordinates* Represent sphygmomanometer readings using cuffs of various widths minus simultaneous readings using a standard cuff on the opposite arm.

*Abscissae* The letters A — G represent [illegible] under-estimation of the blood pressure (compared with the standard cuff) is the same with fat and thin arms. The rate of change of apparent blood pressure with change in cuff width is least with cuffs of 10 — 14 cm. width.

The impression gained from these results is that the errors in measurement of the blood pressure with a cuff which is too small are due to the spread of pressure by the underlying tissues so that the

upon the outside of the artery is less than the pressure within the cuff. Hence the blood pressure is overestimated. The estimated pressure can be brought back to a pressure nearer to that obtained under standard conditions if the cuff is widened (Fig. II 1).

TRANSMISSION OF SPHYGMOMANOMETER CUFF PRESSURE TO THE UNDERLYING ARTERY

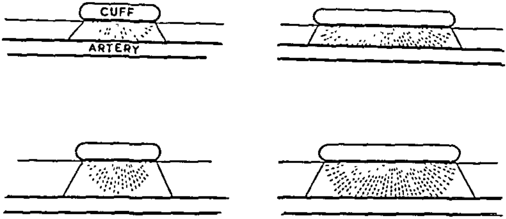



Fig. II 1

[illegible]

approximates to the cuff pressure

Irvine (unpublished observations) prepared a series of arm cuffs of *different widths, viz.: 6, 8, 10, 12, 14, 16 and 18 cm. He noted the* effect of increasing the cuff width upon auscultatory readings of the blood pressure. It was found that if the indirect readings taken with a 12 cm. cuff are accepted as an arbitrary standard, the extent to which the 6, 8 and 10 cm. cuffs overestimated the blood pressure was:

(1) Greater in hypertensives than in normotensives (Fig II 2).
(2) Greater in fat arms than in thin arms (Fig. II 3).
(3) Progressively greater as the cuff decreases in width (Figs. II 2 and II 3).

If, however, the auscultatory readings are made using 14, 16 and 18 cm. cuffs, also compared with the usual 12 cm cuff readings, the extent to which the blood pressure was underestimated was

(1) almost uninfluenced by the level of the blood pressure
(2) almost uninfluenced by the girth of the arm
(3) progressively greater as the cuff increases in width.

Forty-eight persons were studied. In each person the apparent blood pressure measurements using the seven cuffs of different widths were compared with measurements using a standard cuff. There were 12 subjects in each of the four arm girth categories, and in each arm girth category there were four persons with systolic pressures between 100 and 140 mm Hg, four persons with 150 to 190 mm. Hg, and four persons with 200 to 220 mm Hg

measurements show that, with the patient in the horizontal posture,

Southby, 1935; Amsterdam and Amsterdam, 1943; Beckman, 1953). This latter finding is the result of the stream of blood being discharged more directly into the right innominate artery than it is into the left subclavian. The difference in pressure between the two arms is greater when the blood pressure is high than when it is normal.

The suggestion has been made that methods of blood pressure measurement which depend upon compression of arteries by cuffs are less satisfactory in-

... as measured by the direct method may rise 20 to 30 mm. Hg, but by the auscultatory method is unaltered This may be due to the failure of the auscultatory method to register reflected summation waves. It is possible, therefore, that the auscultatory method is an index of central aortic pressure and the intra-arterial method a better index of the local pressure in an artery

Some of the adverse effects of high blood pressure, such as heart failure, probably depend mainly on high pressure in the aorta or other large blood vessels; but other effects, such as arteriosclerosis, affecting the local blood flow of organs such as the brain or kidneys, may depend on the pressures in ...

... of the blood pressure in the brachial artery, but independently of the blood pressure in the artery from which they are derived.

## CASUAL, BASAL AND SUPPLEMENTAL PRESSURES

It is well known that the blood pressure in one and the same individual is variable, and is apt to *fall during* a stay in hospital. The fall may be such that the patient is hypertensive on one occasion and normotensive on another.

Addis (1922) introduced the idea of measuring the blood pressure under basal conditions. In the course of work with Alam I suggested (4, 31) that blood pressures taken under ordinary clinical ... should be called "casual" blood press... diastolic), that pressures taken unde... should be called "basal" systolic a... and that the casual minus the basal readings should be called "supplemental" blood pressures (systolic and diastolic). Thus "casual" blood pressure equals "basal" blood pressure plus "supplemental" blood pressure.

pressure on the segment of artery lying beneath the narrow cuff is exposed to a smaller pressure than the cuff pressure. This error diminishes as the cuff increases in size and probably is no longer important for any size of arm when the cuff has attained 16 or even 14 cm. width.

The error due to using large cuffs is probably of a different kind and due to interference with the production of auscultatory phenomena due to compression of longer stretches of the brachial artery, with consequent increase in the resistance to the flow of blood. It is concluded that there is a cuff width for every arm which is likely to give an approximately correct reading of the systolic and diastolic pressures and that in general this cuff width is 12 cm. for arms of 11½ inches girth or less and a 14 cm. cuff for 11½ inches girth or more.

Rytand and Boyer (1954) found that in general the use of blood pressures taken at the wrist seemed to be satisfactory in patients with gross upper arm obesity.

### Mean Blood Pressure

The mean blood pressure in man may be measured by arterial puncture using a mercury manometer. Any calculation of mean blood pressure from the values of the systolic and diastolic pressures can only be approximate, as the time course of the blood pressure fall from systolic to diastolic varies from person to person.

Sometimes the average of the systolic and diastolic pressures is referred to as the mean blood pressure. Probably the diastolic pressure plus one third of the pulse pressure gives a better estimate

## PRESSURE LEVELS IN DIFFERENT PARTS OF THE BODY

It is well known that in the erect posture the blood pressure in dependent parts of the body is greater than the blood pressure in the arm held at heart level. The difference, however, is not exactly equivalent to the head of the pressure. In the erect posture the blood pressure in the cerebral arteries is some 20 mm. Hg less than the pressure in the arm at heart level. In the standing posture the blood pressure at the ankle may be 100 mm. Hg higher than it is in an arm. It is sometimes overlooked, however, that pressure levels in different parts of the arterial circulation are influenced by factors other than the pressure in the aorta and the effects of gravity. As the blood is in motion, and as pressure waves travel out in systole from the centre to the periphery and are reflected back from the periphery towards the centre, it follows that the intravascular pressure at any given point in the arterial system will be lifted by the crest and lowered by the trough of such pressure waves. The effect of pressure waves will not be equal throughout the arterial system, but will depend on the shape, situation and elasticity of the vessels (Wiggers, 1928). Intra-arterial

[illegible] patient in the horizontal posture [illegible] it is found that if a difference exists it is nearly always the right arm that exhibits a slightly higher pressure (Korns and Guinand, 1933; Southby, 1935; Amsterdam and Amsterdam, 1943; Beckman, 1953). This latter finding is the result of the stream of blood being discharged more directly into the right innominate artery than it is into the left subclavian. The difference in pressure between the two arms is greater when the blood pressure is high than when it is normal.

The suggestion has been made that methods of blood pressure measurement [illegible] pressure as measured by the direct method may rise 20 to 30 mm. Hg, but by the auscultatory method is unaltered. This may be due to the failure of the auscultatory method to register reflected summation waves. It is possible, therefore, that the auscultatory method is an index of central aortic pressure and the intra-arterial method a better index of the local pressure in an artery.

Some of the adverse effects of high blood pressure, such as heart failure, probably depend mainly on high pressure in the aorta or other large blood vessels; but other effects, such as arteriosclerosis, affecting the local blood flow of organs such as the brain or kidneys, may depend on the pressures in somewhat smaller vessels, and upon their state of contraction or dilatation. The blood pressure in small vessels often will vary independently, not only of the blood pressure in the brachial artery, but independently of the blood pressure in the artery from which they are derived.

## CASUAL, BASAL AND SUPPLEMENTAL PRESSURES

It is well known that the blood pressure in one and the same individual is variable, and is apt to fall during a stay in hospital. The fall may be such that the patient is hypertensive on one occasion and normotensive on another.

Addis (1922) introduced the idea of measuring the blood pressure under basal conditions. In the course of work with Alam I suggested [11, 31] that blood pressures taken under ordinary clinical conditions should be called "casual" blood pressures (i.e. casual systolic and casual diastolic), that pressures taken under certain defined basal conditions should be called "basal" systolic and diastolic and that the casual minus the basal readings should be called "supplemental" blood pressures (systolic and diastolic). Thus "casual" blood pressure equals "basal" blood pressure plus "supplemental" blood pressure.

The basal pressure is comparatively constant for the individual. The supplemental pressure is essentially variable and, in contrast to the basal, is defined as that part of the casual pressure which is elevated

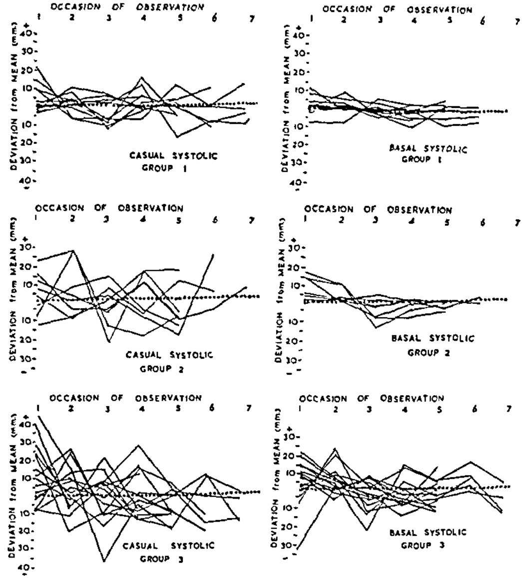



Fig II 4a

The degree of variation from day to day of the systolic blood pressure levels of the subjects in the three groups The levels of the individual readings of each subject are plotted as points above or below a zero line that represents the mean level of that

The subjects were grouped as follows Group I, normal blood pressure levels, Group II, intermediate pressure levels, Group III, hypertensive levels (Kilpatrick, J A, Brit Heart J, 10 48, 1948).

as the result of the patient's physical, metabolic, mental and emotional activity at the time the pressure is measured.

Kilpatrick (1948) made repeated measurements of the basal pressure extending over a number of weeks and has shown that, in healthy normotensives, the basal blood pressure is almost a physiological constant. Whatever the level of the casual blood pressure beforehand, the basal blood pressure, in one and the same person, would be found at

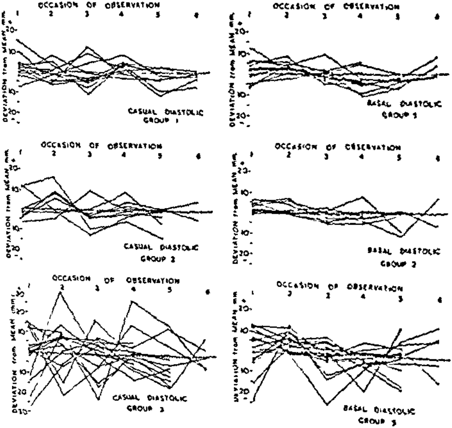



Fig II 4b

The degree of variation from day to day of the diastolic blood pressure levels of the subjects in three groups The casual and basal pressures are shown separately. For details see Fig. II 4a. (Kilpatrick, J A, Brit. Heart J, 10 · 48, 1948).

approximately the same level (Fig. II 4a and b). This leads us to the view that the basal blood pressure is a definite physiological entity; in normotensives it is the comparatively steady ...

blood ...

t1 ...

a ...

we n ...

D ...

tal pressure. As is seen in Figs. II 4a and b the basal blood pressure (both systolic and diastolic) is less variable than the casual blood pressure. It is desirable that we should be determining true basal pressures, because the basal pressure is something to which a definite meaning can be attached. It is the blood pressure which is found when the body is in a state of physical, metabolic and psychological rest. The practice of describing pressures such as "the lowest during a period of bed rest in hospital" as "basal" is misleading, for they are usually well above the basal.

TABLE II 1 — *Comparison of methods of measuring basal blood pressure.* (Smirk, *Brit. Heart J.*, 6:176, 1944)

| Subject | Casual blood pressure | Basal blood pressure by three methods | | |
|---|---|---|---|---|
| | | Method of Cardiological Committees | Method of emotional desensitization | Combination of two methods |
| D | 192/118 | 188/100 | 182/124 | 164/98 |
| C | 122/86 | 122/86 | 110/79 | 106/68 |
| J | 118/54 | 96/58 | 106/52 | 92/54 |
| McN | 98/66 | 106/64 | 94/75 | 96/60 |
| Mu | 130/74 | 132/76 | 110/77 | 122/74 |
| Mo | 104/74 | 98/62 | 94/64 | 80/62 |
| S | 134/90 | 130/90 | 112/80 | 128/88 |
| Wi | 122/66 | 128/68 | 118/55 | 124/66 |
| Ma | 114/78 | 106/78 | 110/76 | 92/78 |
| N | 120/60 | 106/70 | 110/58 | 94/61 |
| O | 122/68 | 112/68 | 116/58 | 110/65 |
| W | 130/76 | 114/74 | 116/68 | 112/70 |
| Me | 116/72 | 92/60 | 106/68 | 90/65 |
| Average | 124 8/75.5 | 117.7/73.4 | 114.2/71.8 | 108.5/69.9 |

A study of the basal and supplemental pressures in a series of 50 young normal males indicated that the systolic basal pressure might vary from 80 to 125 and the supplemental pressure from 3 to 30 mm. Hg.

Addis (1922) used the term basal blood pressure to indicate blood pressure levels measured in patients before they rose from bed in the morning. These levels were lower than those recorded later in the day. The basal pressure as defined by Addis is not, however, the lowest pressure which can be obtained under conditions of rest in normal individuals. The British and American Cardiological Societies (1939) recommended that the pressure to be accepted as the basal pressure should be taken in the morning as Addis recommended, but that the patient should be prepared as for a basal metabolic rate. Alam and

Smirk (1943) recommended that the patients should be deliberately habituated to the presence of the observer and his sphygmomanometer for, unless this special precaution was taken, the presence of the observer and the act of measuring the blood pressure would often be sufficient to cause appreciable rises in the arterial level. Later the method of the British and American Cardiological Societies was ... with the procedure of emotional desensitization (Table II 1). ... levels of the blood pressure than ... procedures used separately, has become our standard procedure for measuring basal blood pressures.

## Determination of Basal Blood Pressure

If a true basal blood pressure is to be obtained all anxiety and tenseness on the part of the patient must be allayed and the following steps should be taken:

(1) The patient must be reassured beforehand that *measurement of the blood pressure would not be the prelude to any unpleasant* happenings, the object of the test being to measure the blood *pressure* under conditions of rest. (It need hardly be added *that a basal state* will not be obtained if the patient is informed that "*it will help us to* decide about your future prospects".)

(2) The ... repeatedly ... observer ... during the measurement and for the patient to keep the mind blank and *avoid thinking* over personal problems or difficulties.

(3) It is desirable for the patient to have slept well on the night before the test and our procedure of late has been to administer a sedative, ordinarily 1½ to 3 gr. of pentobarbital.

(4) *In the* morning the patient uses a urinal or bed pan if necessary, soon after waking No *food is given but it* is now our practice to give an additional sedative, 1½ *or occasionally 3* gr. of pentobarbital. The patient should, *for preference, sleep in* the room where the basal blood pressure is to be taken *next morning*, otherwise the patient's bed is moved to a warm single *room, and the* patient asked to remain quietly at rest

(5) The observer now ... not converse and proceed ... minute intervals for 20 ...

*It* is important to note *that* restlessness on the part of the observer, displays of medical equipment ...

... Where technicians are used ... measure basal blood pressures they should be told that any ...

to reprimand a patient for restlessness and any show of impatience on their part is likely to raise the blood pressure above the basal level.

(6) The average of the two lowest blood pressures is accepted as the basal blood pressure.

Not infrequently the combined effect of the sedative and frequent monotonous repetition of blood pressure measurements lead to sleep. Usually the blood pressure level is not appreciably lower when the patient sleeps under these conditions than when awake but basal and relaxed. On a number of occasions I have witnessed experiments in which the blood pressure during light anaesthesia was only a few mms. below the basal pressure.

The importance of habituation to the presence of the observer and his sphygmomanometer is indicated in some observations [4] in which a near basal blood pressure was obtained by half an hour of rest in the presence of an observer who, repeatedly and at half-minute intervals, made measurements of the blood pressure. When, however, a second observer walked into the room and measured the blood pressure this would always rise to a higher level. It should be pointed out that trivial stimuli induce larger blood pressure rises when the initial blood pressure is basal than when it starts at an ordinary casual level

Sometimes although the conditions of measurement seem to be satisfactory a true basal state may not be attained and this may not be immediately apparent to the observer Several examples have occurred in our clinic. One patient had been kept awake by ulcer pain Another patient who had previously exhibited a low basal blood pressure had been told that basal blood pressures were a prelude to surgery On the next occasion the blood pressure of this patient would not fall to basal levels. He was then told that in his case there was no question of surgery, and further measurements showed a return to the original low basal readings. Kilpatrick (1948) made repeated measurements of the basal blood pressure in several patients and cites two similar experiences He says: "The most remarkable divergences from the usual basal level were shown when concealed emotional factors were present One hypertensive subject had received by letter disturbing news about her son's conduct. The "basal" pressure next morning was 60 mm. higher than usual, and only after prolonged questioning was the cause revealed In another instance the subject, a soldier, showed slowly increasing levels of "basal" pressure. Interrogation failed to reveal any [illegible] to the subject but it was found by chance that he was [illegible]

pressure readings returned to their previous level." In such cases it must be emphasized that there was failure to obtain a basal pressure

*Some emphasis may be laid on the fact that it is repeated measurement by the same person on the same occasion that produces the maximum degree of habituation to the process of blood pressure measurement.* Adequate emotional desensitization will seldom be obtained even if the same observer measures the blood pressure daily in the wards. The blood pressure will, of course, become lower as the patient gets used to the ward and to the medical staff but rarely does the blood pressure fall as much during several weeks in hospital as it does under the condition set out for basal blood pressure measurement.

In a series of 60 normal subjects (Smirk, 1944) the basal and supplemental pressures seemed to be almost independent variables in

the sense that the possession by an individual of a high basal pressure neither increased nor appreciably diminished the expectation of that ... there was a ... measurements made at a later date was statistically significant.

## "NORMAL" BLOOD PRESSURE

The question of what is "normal" blood pressure is of great interest and some complexity. The term "normal" is used with more than one meaning and an attempt at clarification at once reveals some fundamental problems for which a solution must be sought. Broadly speaking, "normal" blood pressure may mean one of two things:

(1) That the blood pressure level has been determined solely by the action of physiological processes.

(2) That the sphygmomanometer reading is satisfactory in terms of criteria still to be defined.

An example may help Of three apparently healthy men, age 35, the first two have blood pressures of 105/75 and 130/85 respectively. The man with the lower pressure develops acute nephritis and his pressure rises from 105/75 to 130/85; and as he recovers it falls back to 105/75. According to the first definition the pressure 130/85 was abnormal in the man who had nephritis because 25/10 mm. Hg blood pressure elevation was attributable to a pathological process. The same blood pressure is normal in the man who remained healthy because no pathological process was discovered.

The third man, at a life insurance examination, is found to have a blood pressure of 200/105, but no other defect. He is diagnosed as hypertensive in terms of the sphygmomanometer reading. Concerning the third man we may say:

(1) Investigation has revealed no evidence of a pathological process, and it is unknown whether one is present or not.

(2) The level of the blood pressure is abnormal in the sense of being unusually high at the time it was taken.

(3) There is a high expectation that the third man will exhibit evidence of pathological change within 10 years or less, and will ultimately die from one of the disorders known to be associated with unusually high blood pressures.

We use the blood pressure level not only as clinical evidence of present illness but also as evidence of the expectation of illness in the future. We must, therefore, attempt to say what is a "normal" and what is an "abnormal" level of the blood ... other ... at a stage when is not ... ressure of 200/105 ... To be 6 ft. 3 ins.

in height is much more unusual than to die of hypertension, but we do not describe this height as pathological, because it is not frequently associated with disability attributable to height. High blood pressures unassociated with manifest pathology are accepted as abnormal because in practice they often cause illness later. A valuable approach to this problem comes from Master et al. (1952) who describe a blood pressure as abnormal when it surpasses the limit of 1.282 S.D. above or below the mean for the particular age and sex. The figure ± 1.282 S.D. includes 40 per cent of all observations on either side of the mean. Master makes it quite clear that blood pressures within *the limits so defined are not to be regarded as ideal pressures* but only as normal in the sense of being usual levels of pressure, a patient having pressures within these limits being a person who is not distinguished by his blood pressure level as being different from the average.

The ideal pressure is another thing. It has been shown beyond dispute that persons whose blood pressures are distinctly below the average for their age and sex, in young persons often in the region of 110/70, are much less likely than the average to die from cardiovascular disease consequent upon hypertension in later life [1, 2, 6, 29, 31]. The high incidence of developed hypertension and of ultimate death from cardiovascular disabilities in people whose blood pressures are above the mean pressure for their age and sex, but still within the range defined by Master et al., makes it a little difficult to be satisfied with the description of such pressures as "normal". It is, however, quite justifiable to describe such pressures to our patients as within *average* limits. Such statements, which help in that they form a basis for reassurance of anxious patients and relatives, must not be allowed to obscure the fact, made very clear by Master et al., that blood pressures which lie within the upper reaches of their average range are not ideal.

The danger of all surveys is that a statistical study of blood pressures which have been taken under one set of conditions may be used as a standard by which to interpret the significance of individual blood pressures taken under quite different conditions. There is the tacit assumption that a person has *a blood pressure*, that figures can be found which express in mm. of mercury *the blood pressure* of the individual and that these figures can then be looked at to see if the blood pressure is "normal"

When the blood pressure is ideally normal or very high the terms normotensive and hypertensive can be used; but when the blood pressure is of intermediate magnitude and fluctuates between, say 140/90 and 190/110, it is evident that the boundary between normal and high casual blood pressure cannot be decided on a simple numerical basis. The evidence for this statement has been strengthened by the

results of a population survey of casual blood pressure variations, with measurements made under defined conditions (Chapter III).

## BASAL AND SUPPLEMENTAL PRESSURES IN HYPERTENSION

When repeated measurements are made, the basal blood pressure does not appear to be as constant in the hypertensive as it is in the normotensive (Fig. II 4a and b). Perhaps this difference is an expression of the greater difficulty in obtaining fully basal conditions in patients with hypertension or it may be an expression of the greater vascular reactivity of these patients. Favouring the former view is an observation by Kilpatrick (1948), that with repeated measurements slightly lower values for basal blood pressure are obtained in the later readings (Fig. II 4a and b). There are, however, alterations in the basal pressure which do not depend on failure to obtain basal conditions. The basal blood pressure may be reduced in febrile states and following surgical procedures, even when there is no shock. In the hypertension of acute nephritis the basal blood pressure falls when the blood pressure returns to normal following recovery. The same occurs with recovery in most patients with the hypert[illegible]

of [illegible]

ma[illegible] comparatively low basal pressure with [illegible]

[illegible]

[illegible] having either a high or a low supplemental pressure and vice versa. It is very well known that when a patient with high blood pressure is admitted to hospital and becomes habituated to the normal ward routine and is rested, the casual blood pressure tends to fall and may be appreciably diminished. It appears from the results of Smirk (1944) and of Kilpatrick (1948) that this is due mainly, perhaps entirely, to diminution of the supplemental blood pressure.

In our view the determination of the basal blood pressure is of considerable importance in hypertensive patients because it indicates the lowest level of the blood pressure which is obtained under natural conditions of rest. Where the basal blood [illegible]

[illegible] the basal blood pressure is [illegible] the strain on heart and blood vessels is of a more continuous kind. It will be seen in Chapters V and XXI that where [illegible] are equal the patients [illegible]

pr[illegible]

pa[illegible]

The mortality among patients with high basal blood pressures is very much greater than among patients with low basal blood pressures. The basal blood pressure is a much better index of the severity and of the prognosis of hypertension than the casual blood pressure. With the basal pressure it should be easier to define the more accurately the boundary zone between "normal" and "abnormally high" blood pressures.

## References

1 Actuarial Society of America and the Association of Life Insurance Medical Directors. Blood Pressure Study, 1939.

2 Actuarial Society of America and the Association of Life Insurance Medical Directors. *Supplement to Blood Pressure Study, 1941.*

3 Addis, T. Blood pressure and pulse rate levels, Arch. intern. Med, 29: 539, 1922.

4 Alam, G. M., and Smirk, F. H. Casual and basal blood pressures. I. In *British and Egyptian men. Brit. Heart J., 5: 152, 1943a.*

5 Amsterdam, B., and Amsterdam, A. L. Disparity in blood pressures in both arms in normals and hypertensives and its clinical significance; A study of 1,000 normals and 272 hypertensives N.Y. St J. Med., 43: 2294, 1943

6 Association of Life Insurance Medical Directors and the Actuarial Society of America. Blood Pressure, Report of the Joint Committee on Mortality, 1925.

7 Beckmann, A. Blutdruck-Seitendifferenzen an den oberen Extremitaten Dtsch. med Wschr, 78: 218, 1953.

8 Committee for the Standardization of Blood Pressure Readings of the American Heart Association and of the Cardiac Society of Great Britain and Ireland Standard Method for taking and recording blood pressure readings J Amer. med. Ass, **113**: 294, 1939.

9 Fishberg, A. M. Hypertension and nephritis. Lea and Febiger, Philadelphia, 1954, 5th edn

10 Gaertner, G. Über einen neuen Blutdruckmesser (Tonometer). Wien. med. Wschr., *49: 1412, 1899*

11 Hamilton, W F., Woodbury, R. A., and Harper, H T., Jr Physiologic relationships between intrathoracic, intraspinal and arterial pressures J. Amer. med. Ass, **107**: 853, 1936.

12 Hensen, H *Beiträge zur Physiologie und Pathologie des Blutdrucks.* Dtsch. Arch. klin. Med., 67: 436, 1900

13 Janeway, T. C The influence of the soft tissues of the arms on clinical blood-pressure determinations Arch intern. Med, 3: 474, 1909.

14 Kilpatrick, J. A. The variation of casual, basal and supplemental blood pressures in health and in essential hypertension Brit Heart J, **10**. 48, 1948.

15 Korns, H M., and Guinand, P H Inequality of blood pressure in the brachial arteries with especial reference to disease of the arch of the aorta J. clin. *Invest., 12· 143, 1933.*

16 Kotte, J H, Iglauer, A, and McGuire, J Measurements of arterial blood pressure in arm and leg, comparison of sphygmomanometric and direct intra-arterial pressures with special attention to their relationship *in aortic regurgitation.* Amer Heart J, 28: 480, 1944

17 LANDOIS, L. Die Lehre vom Arterienpuls nach eigenen Versuchen und Beobachtungen dargestellt A. Hirschwald, Berlin, 1872. Cited by Master, A. M, Garfield, C. I, and Walters, M. B, Normal blood pressure and hypertension, Lea and Febiger, Philadelphia, 1952.

18 MAREY, E. J. Recherches sur le pouls au moyen d'un nouvel appareil [illegible]

19 MAR [illegible]

20 MASTER, A. M, GARFIELD, C. I., and WALTERS, M. B. Normal blood pressure and hypertension. Lea and Febiger, Philadelphia, 1952

21 Mosso, A Sphygmomanomètre pour mésurer la pression du sang chez l'homme. Arch Italiennes de Biologie, 23: 177, 1895

22 MUDD, S. G, and WHITE, P. D The auscultatory gap in sphygmomanometry Arch intern. Med, 41: 249, 1928

23 NORRIS, G W Blood pressure· Its clinical applications. Lea and Febiger, Philadelphia, 1917.

24 PHILADELPHIEN, M A Le sphygmométrographe imaginé C. R. Soc. Biol. (Paris), 48 199, 1896

25 RAGAN, C, and BORDLEY, J Accuracy of clinical measurements of arterial blood pressure, with note on auscultatory gap Bull Johns Hopk. Hosp, 69. 504, 1941.

26 RIVA-ROCCI, S Un nuovo sfigmomanometro Gazz. méd. di Torino, 47: 121, 1896 Cited by Master, A M, Garfield, C. I., and Walters, M. B. Normal blood pressure and hypertension. Lea and Febiger, Philadelphia, 1952.

27 RIVA-ROCCI, S De la ménsuration de la pression artérielle en clinique. Press méd, 22 307, 1899

28 ROBERTS, L N, SMILEY, J R., and MANNING, G. W A comparison of direct and indirect blood pressure determinations. Circulation (N.Y.), 8 232, 1953

29 ROBINSON, S C, and BRUCER, M. Range of normal blood pressure — A statistical and clinical study of 11,383 persons Arch. intern. Med, 64. 409, 1939

30 RYTAND, D. A, and BOYER, S H Auscultatory determination of arterial pressure at wrist and ankle J clin Invest, 33: 961, 1954.

31 SMIRK, F H. Casual and basal blood pressures IV. Their relationship to the supplemental pressure with a note on statistical implications. Brit Heart J., 6· 176, 1944.

32 SOUTHBY, R Some clinical observations on blood pressure and their practical application, with special reference to variations of blood pressure readings in two arms Med. J Aust, 2: 869, 1935.

33 STEELE, J M Comparison of simultaneous indirect (auscultatory) and direct (intra-arterial) measurements of arterial pressure in man. J Mt Sinai Hosp., 8· 1042, 1942

34 Transactions of the International Congress on Life Assurance Medicine, London, 1935

35 VAN BERGEN, F H, WEATHERHEAD, D S, TRELOAR, A. E., DOBKIN A B, and BUCKLEY, J. J Comparison of ind[illegible] of meas[illegible]

36 VIERORDT, [illegible] Cited b[illegible], and Walters, M B Normal blood pressure and hypertension, Lea and Febiger, Philadelphia, 1952

37 VON BASCH, S. Ueber die volumetrische Bestimmung am Menschen. Wien. med. Jahrbuecher, 1876. Cited by Master, A. M., Garfield, C. I., and Walters, M. B. Normal blood pressure and hypertension. Lea and Febiger, 1952.

38 WALDENBURG, L. Die Messung des Pulses und des Blutdrucks am Menschen. A Hirschwald, Berlin, 1880. Cited by Master, A. M., Garfield, C. I., and Walters, M. B Normal blood pressure and hypertension, Lea and Febiger, Philadelphia, 1952.

39 WIGGERS, C. H. The pressure pulses in the cardiovascular system Longmans, Green & Co., London, 1928.

## CHAPTER III

# NATURAL HISTORY AND ECOLOGY OF HIGH AND LOW BLOOD PRESSURE

In this chapter it is proposed to consider some of the factors which influence the results of population surveys of blood pressure, and to report some observations on basal and near-basal blood pressures.

In many parts of the world the levels of the blood pressure and the incidence of hypertension are less than in the United States of America, Europe and Australasia. The accessible information has been reviewed.

## RELATION OF BLOOD PRESSURE TO AGE

That, at least in certain communities, the mean blood pressure rises with age was known to Janeway (1904) and Brunton (1909) and has been amply confirmed. The changes in blood pressure level with age have been reported by a number of authors [18, 47, 58, 76, 99, 103, 125, 136, 151, 154] and some of these are summarized in Figs. III 3a and b.

At birth, in full-term infants, the systolic blood pressure is of the order of 50 mm Hg [121, 134]. Reis and Chaloupka (1923) give an average systolic pressure of 43 mm. and Rucker and Connell (1924) give 54 mm The average diastolic pressure is given by Rucker and Connell as 40 mm By the tenth day the systolic blood pressure has risen to about 70 mm. Hg. The diastolic pressure does not increase as much as the systolic and, according to Rucker and Connell, an average level of 42 mm. is attained about the tenth day. Even at this early age, higher blood pressures are seen with larger birth weights, and in premature infants the blood pressures are below those taken in full-term infants.

In children clinically useful blood pressure measurements may be [illegible]

[illegible] effect on the apparent blood pressure level.

Blood pressures in somewhat older children are given by Judson and Nicholson (1914), Stocks and Karn (1924), Faber (1927) and Graham, Hines and Gage (1945) The average systolic and diastolic blood pressures rise with age between the seventh and twentieth year (Fig. III 1)

In adults the statistics relating blood pressure to age are influenced by the inclusion of more hypertensives in older age groupings. Even when frank hypertensives are omitted there remains a strong relationship between age and the mean blood pressure in the British, Western European and American statistics. Some evidence will be referred to later that among East African and American Indians, living in a primitive way, the mean blood pressure may fall after the age of 40 (Faught, 1916; Donnison, 1929).

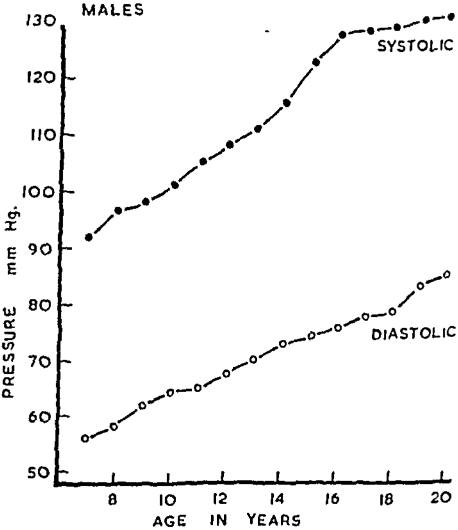



Fig III 1

*Average systolic pressure at different ages (males) Average diastolic pressure at different ages (males). (Stocks, P., and Karn, M. N, Cambridge University Press, 1924).*

An investigation of the extent to which rise of blood pressure with age may be attributed to the inclusion of hypertensives involves a delineation of the frontiers of normal and high blood pressure. An obvious difficulty is that there exists no simple way of distinguishing

(if indeed there is a distinction) between small or moderate increments of blood pressure due to the early beginnings of hypertension and blood pressure increases of equal magnitude due to physiological processes. It is unlikely therefore, that the removal of frank hypertensives from a statistical analysis will eliminate the effect of "pre-hypertensives" whose blood pressures have not risen sufficiently to warrant elimination.

Symonds (1923), in a life insurance study, noted the effect of removing all risks with pressures over 140 systolic. This reduced the difference in systolic blood pressure, between the youngest and the oldest age period, from 12 mm to 8.6 mm. Robinson and Brucer (1939) take an extreme view. They consider that the "normal" range of systolic blood pressure for men and women is 90 to 120 mm and of diastolic pressure 60 to 80 mm. They say that the normal blood pressure is attained at adolescence and maintained throughout life, except for a slight rise about the age of 20 ... [illegible]

for men as +0.02±0.01 [illegible]
pressures 0.09±0.01 for men and 0.22±0.01 for women.

Altogether it may be concluded that the rise with age becomes less conspicuous if the "hypertensives" are eliminated at any level at or above 140/90. The statistical justification for an arbitrary truncation at the level of 140/90 has been strongly criticized by Treloar (1940) and by Hamilton et al. (1954a). While one must agree that there is no justification for expressing the boundary between normal and abnormal numerically, it is of interest to know that the lower the first observed blood pressure, the less is the chance of the blood pressure rising with advancing years.

The general ... [illegible]

... pressures of 2,031 outpatients attending the varicose vein, skin, orthopaedic, fracture and dental clinics. They noted the steeper increase of the mean blood pressure with age in the female and the absence of any sharp distinction between hypertension and normotension. They give frequency distribution diagrams, including all patients. Their distribution diagrams are very similar to those of Master et al. (1952) who summarize observations on 74,000 individuals representative of a healthy working population in U.S.A. It is evident from Master's distribution curves (Fig. III 2) that in females there is a steeper increase of the mean and also of the modal blood pressure with age than in males. It is readily seen in the graphs that, although more hypertensives are included as age advances, the increase in the blood pressure with age does not depend solely ... this, for if all patients with ... Hg are excluded.

conclusion is reached if all persons with blood pressures higher than 140 or 130 systolic are excluded. Similarly, if all persons with diastolic pressures higher than 90 mm. Hg are excluded, the average diastolic

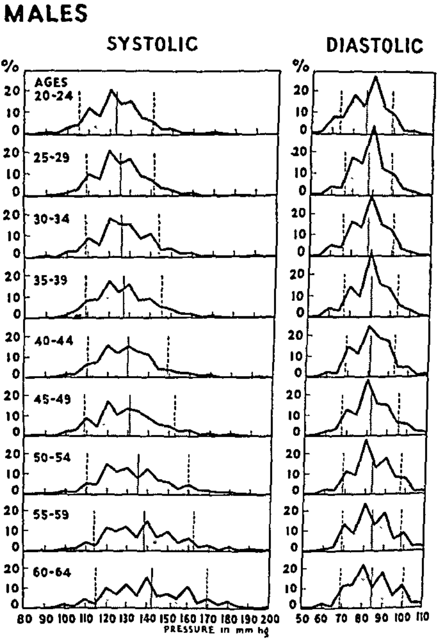



Fig III 2a

Frequency distribution curves of entire material (in 5 year age groups) employed to establish new limits of blood pressure for males (Master, A M., Garfield, C. I, and Walters, M B, Lea and Febiger, Philadelphia, 1952)

pressure also rises with age. In the females at least it appears that the number with systolic blood pressures under 110 decreases with advancing years. The same impression is gained from inspecting the results of

Gover (1948), Hamilton et al. (1954a), Holmgren (1955) and of Weiss (1951) who published extensive data from Hamburg, Germany.

Statistical surveys are influenced by the conditions under which

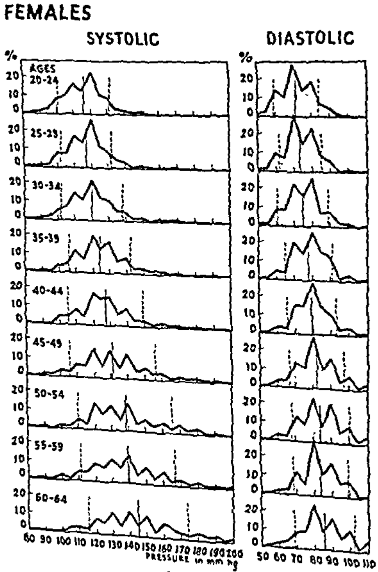



Fig III 2b

Frequency ...

the blood ...
fc
ш

... reduced the percentage of systolic pressures ... decrease the

in excess of 140 mm. Hg from 16.2 to 9. Where emotions, including normal emotions, are concerned the difference between a friendly and a formidable doctor or between a homely and a forbiding examination room may be represented by a difference of 20 to 40 mm. Hg

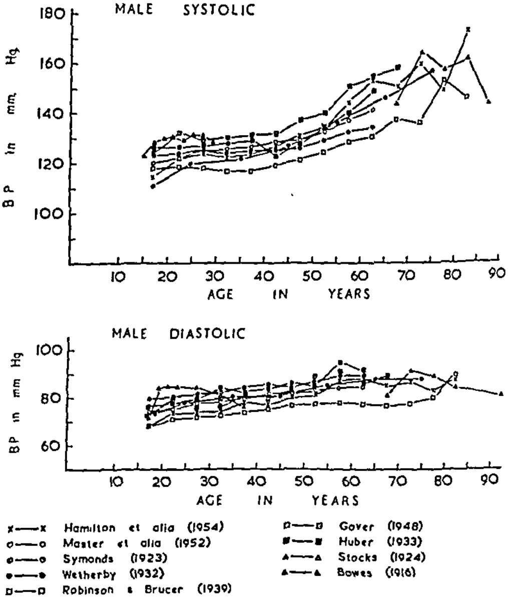



Fig III 3a
Relationship of casual blood pressure to age in males (Various authors)

systolic and 10 to 20 mm. diastolic. Measurements of the blood pressures taken soon after the patients make contact with the doctor are often higher than those taken when the patients have got used to the doctor and his office.

The effect on blood pressure of the circumstances surrounding blood pressure measurements were the subject of a population survey on 370 persons (Veale et al., 1956). Blood pressures were measured under the following conditions: patients were chosen who were attending

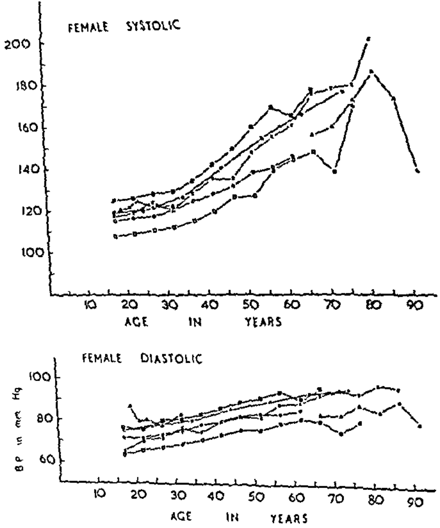



Fig III 3b
Relationship of casual blood pressure to age in females (Various authors).

hospital clinics unlikely to attract patients with unusual blood pressures, and a number of blood pressure measurements were made on each person under defined conditions.

E

1. The first casual blood pressure measured which, as an average, and also in most individuals, gave the highest reading, was obtained in the course of a normal clinic attendance (skin, orthopaedic, etc.). Patients were asked to step behind a screen and, without explanation, the blood pressure was measured (first casual blood pressures in Fig. III 4a and b) and recorded. The pressure recorded was the first pressure

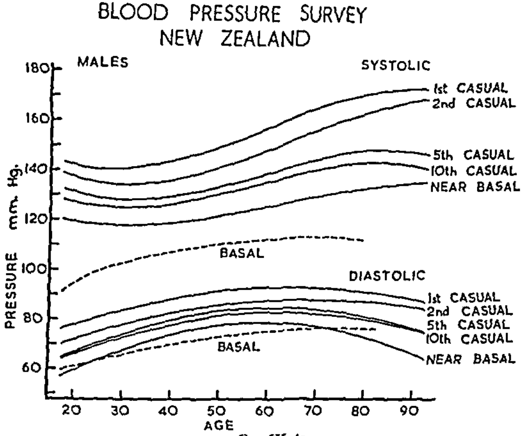



*Fig. III 4a*

Relationship of casual blood pressure to age in males — effect of making repeated blood pressure measurements on blood pressure statistics (See text and Fig. 7).

measured and no attempt was made to obtain a lower reading by repetition of the measurement, and no attempt was made either to intimidate or to reassure or otherwise to provide an unusual stimulus situation.

2. After obtaining this first casual blood pressure the patients were informed that a survey of blood pressure levels was being made, the whole procedure was explained, and they were asked if they could conveniently make a morning attendance at a special outpatient department for us to determine the near-basal blood pressure. Not the slightest pressure was used as annoyance or unwillingness to attend would be likely to affect the result obtained. Approximately half of the

patients found it convenient to do this. On arrival at the clinic patients were not kept waiting, they were asked to lie on a comfortable couch in a single room, the blood pressure was measured without a preliminary rest period (2nd casual blood pressures in Fig. III 4a and b) and

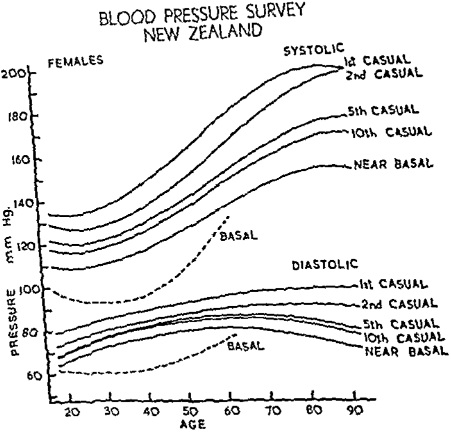



Fig. III 4b

Relationship of casual blood pressure to age in females — effect of making repeated blood pressure measurements on blood pressure statistics. (See text and Fig 7).

all subsequent blood pressures were recorded and numbered in succession, e g. 5th casual, 6th casual, etc. With repeated measurement of the blood pressure at half minute intervals, the doctor being present throughout, we found that the blood pressure falls much more than it does when the doctor enters and takes only a few measurements after the patient has been resting The progress of the blood pressure fall was recorded.

3 The lowest blood pressure recorded at the clinic within a period of approximately 25 minutes of combined rest and habituation to the presence of the doctor and procedure of measurement, is described as the near-basal blood pressure.

4. In a number of other patients the blood pressure was determined in hospital by the more rigid basal blood pressure technique referred to in Chapter II. In a few patients both near-basal and basal blood pressures were obtained.

### Usual Range of First Casual and Near-Basal Blood Pressures

The approach to the patients which we used when determining the first casual pressure and the near-basal pressure do not differ in any remarkable way from the various procedures which have been adopted by others who have collected statistics on blood pressure levels; yet, as already mentioned, in one and the same group of individuals, the averages of our first casual pressures for each age group lie above, and the averages of our near-basal readings from these same individuals lie below, the usual published statistics obtained on other populations of European origin as seen in Figs. III 3, 4 and 7.

The blood pressures measured over the 25-minute period were taken at specified times so that in between the curve for high casual readings and the curve for near-basal readings our figures enable us to draw a series of intermediate curves, the levels of which correspond quite closely with some of those already published (see Fig. III 4 a and b).

*The average rises with age in the near-basal and basal blood pressures* are less than the rises of the casual blood pressures. The supplemental pressure (casual minus basal) also rises with age.

### Relationship of Near-Basal and Basal Blood Pressures

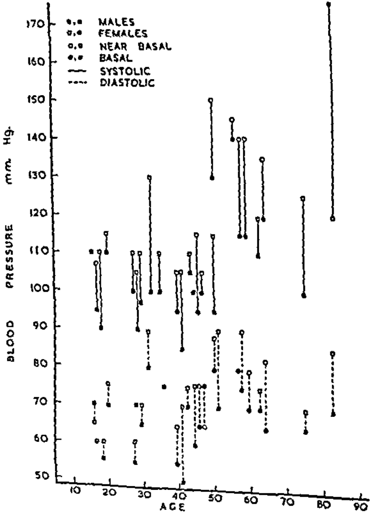
The procedure used for determination of the near-basal blood pressure represents our attempt to obtain an approximation to the basal blood pressure by a simple technique which would make the collection of extensive data practicable. It was found that the basal blood pressure level measured after a night's rest in hospital, using the technique already referred to in Chapter II, *lies distinctly below the* near-basal level (Fig. III 4c).

In a number of subjects a repetition of the test was made and, although variations were noted when repeating the casual blood pressures, the near-basal blood pressures were found to be comparatively constant in one and the same person. Kilpatrick (1948) made a similar observation with repeated measurements of the basal blood pressure (Fig. II 4). He noted that in normals the basal blood pressure was practically a physiological constant

In the course of our investigation a number of patients undergoing near-basal or basal blood pressure tests slept during the period while the blood pressures were being taken. The blood pressure did not fall further when the patient slept, in either case. The average level of the near-basal blood pressure of those patients (all ages) who slept was 121.3 mm. Hg, and of those who did not sleep was 122.8 mm. Hg.

This is a small difference. It seems very likely, therefore, that the differences between our near-basal blood pressures and our basal blood pressures are not often due to failure to allay apprehension or to other differences in the emotional state.

RELATION OF NEAR BASAL AND BASAL PRESSURES




See text

Fig III 4c

The near-basal blood pressure represents a state in which the psychological stimulus provided by the doctor and his sphygmomanometer has been removed, but supra-basal metabolic activity and

the effect of walking or driving to the clinic have raised the blood pressure above its basal level.

### Relationship between Individual Pressures and Statistical Curves

Surveys of the type we have conducted have led to the conclusion that the average blood pressure rises with age. In our survey we find that between the ages of 50 and 80 the *average* range of the blood pressure measurements in the course of one day is about 35 to 40 mm. Hg systolic, and between ages 20 and 50 is about 20 to 25 mm. Hg

REPETITION OF BLOOD PRESSURE MEASUREMENT AFTER FIFTEEN YEARS OR MORE

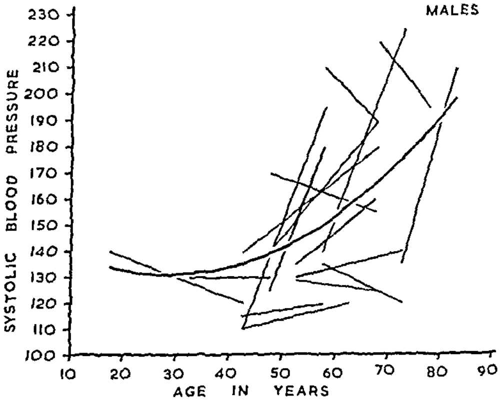



Fig III 6a

Repetition of blood pressure measurement after 15 years or more in males. Each straight line records the change in a single patient A fitted curve has been drawn.

systolic. The variation is about 20 times the annual increase in the mean blood pressure of people in approximately the same age group This makes it clear that occasional measurements of the casual blood pressure, made at intervals over a number of years in one and the same person, must not be expected to follow a curve similar to that which describes the behaviour of a mean of many individuals In the

individual a small rise with age would be obscured by the large changes which are due to temporary fluctuations in the physical and emotional state of the individual, and which do not usually indicate any lasting change in his state of health.

There is, however, good evidence that nearly all persons who live beyond 60 years have a higher blood pressure than they had in youth.

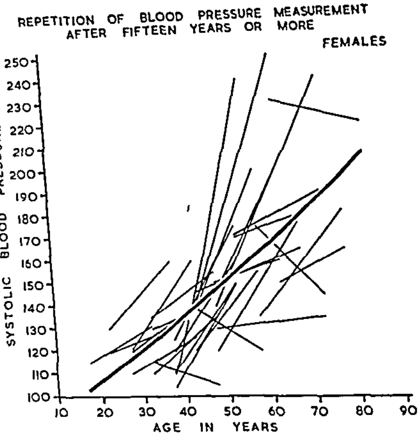



Fig III 5b

Repetition of blood pressure measurement after 15 years or more in females Each straight line records the change in a single patient. A fitted curve has been drawn.

Of the 44 male patients under 25, 10 had first casual systolic blood pressures of over 150 mm. Hg. Of 47 male patients over 60, 35 had pressures above 150 mm Hg. Hence the expectation is that most pressures have risen from below to above 150 mm Hg. In females the difference is more striking. Of 34 females under 25, 4 *had a first* casual systolic blood pressure exceeding 150 mm. Hg and 39 out of 43 over 60 had a first casual systolic blood pressure above 150 mm. Hg. Similar evidence leads to the conclusion that the near-basal blood

the effect of walking or driving to the clinic have raised the blood pressure above its basal level.

## Relationship between Individual Pressures and Statistical Curves

Surveys of the type we have conducted have led to the conclusion that the average blood pressure rises with age. *In our survey we find that between the ages of 50 and 80 the average range of the blood* pressure measurements in the course of one day is about 35 to 40 mm *Hg systolic, and between ages 20 and 50 is about 20 to 25 mm. Hg*

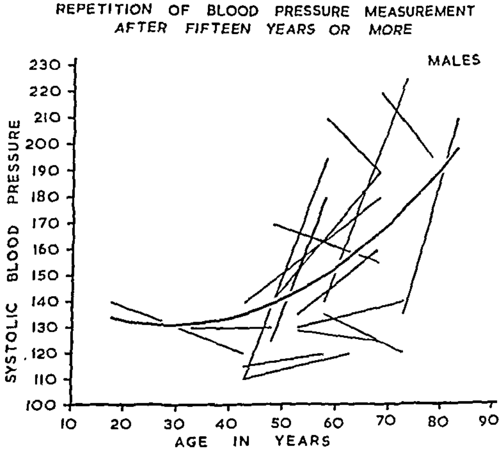



Fig III 5a

Repetition of blood pressure measurement after 15 years or more in males Each straight line records the change in a single patient A fitted curve has been drawn

systolic. The variation is about 20 times the annual increase in the mean blood pressure of people in approximately the same age group This makes it clear that occasional measurements of the casual blood pressure, made at intervals over a number of years in one and the same person, must not be expected to follow a curve similar to that which describes the behaviour of a mean of many individuals. In the

individual a small rise with age would be obscured by the large changes which are due to temporary fluctuations in the physical and emotional state of the individual, and which do not usually indicate any lasting change in his state of health.

There is, however, good evidence that nearly all persons who live beyond 60 years have a higher blood pressure than they had in youth.

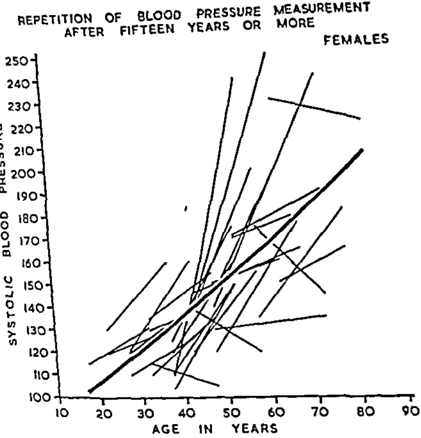



Fig III 5b

Repetition of blood pressure measurement after 15 years or more in females Each straight line records the change in a single patient A fitted curve has been drawn.

Of the 44 male patients under 25, 10 had first casual systolic blood pressures of over 150 mm. Hg. Of 47 male patients over 60, 35 had pressures above 150 mm Hg. Hence the expectation is that most pressures have risen from below to above 150 mm. Hg. In females the difference is more striking. Of 34 females under 25, 4 had a first casual systolic blood pressure exceeding 150 mm. Hg and 30 out of 43 over 60 had a first casual systolic blood pressure above 150 mm. Hg. Similar evidence leads to the conclusion that the near-basal blood

pressure of most individuals rises with age. There is, however, no certainty that the rises are physiological and we cannot draw the conclusion from our population survey that the rise is gradual over the years.

A further survey was made (Fig. III 5) of 49 hospital inpatients of various ages who had had several blood pressure measurements spread over 15 or more years. It will be seen that the blood pressure of an individual usually rises in 15 years, but there are many exceptions. The mean blood pressures of this hospital series rise with age in much the same way as in other surveys, but the blood pressures of individual patients are often a long way from the mean. Hypertension may develop gradually or become established within a few years.

## THE RELATIONSHIP BETWEEN BLOOD PRESSURE LEVEL, OBESITY, WEIGHT, HEIGHT, AND BUILD

### Obesity in Relation to Body Weight

Many observations have been published relating obesity to blood pressure levels and to the incidence of high blood pressure. In almost all studies of obesity the body weight, or the body weight related to the height, has been used as an index of obesity. Corrections may be made for the effects of increased arm girth. In crude statistics there is an important correlation between body weight, level of blood pressure and the incidence of hypertension. Observations have been made also on body build. The circumference of the chest above nipple level in men (or a little higher to avoid breast tissue in women) divided by the height, has been used as an index of body build by Robinson and Brucer (1940). The authors describe the following body build types:-

*Linear build* = *Chest: height ratio less than 0.50*
Linear intermediate build = Chest: height ratio between 0.50 and 0.54
Lateral intermediate build = Chest: height ratio between 0.55 and 0.59
Lateral build = Chest: height ratio 0.60 and over.

There is a strong statistical correlation between overweight and lateral build on the one hand and between underweight and linear build on the other. It follows, therefore, that a series of persons selected for overavera [illegible]
of lateral [illegible]
persons o [illegible]
that a statistical correlation established in the first place between blood pressure levels and body weight might in fact be dependent on a relationship between body build and body weight. In order to decide whether body build and body weight have separate effects upon the blood pressure level and the incidence of hypertension, it becomes

necessary to study the effect of overweight and underweight in persons of the same body build. A corresponding difficulty arises in connection with study of the relationship between height and blood pressure. Among tall people there are a larger proportion of persons of linear build and among short people a larger proportion of persons with lateral build. Hence it follows that in considering the relationship between height and blood pressure it is desirable to study the effects of height within a uniform body build group. That is to say, to study the blood pressure level and incidence of hypertension among short persons as compared with tall persons, first in a group of persons of lateral build and second in a group with linear build.

It will be seen from what follows that there is much information *concerning body* weight and hypertension but in only a few of these has a study been made separately of the effects of body weight and body build.

## Effect of Obesity on Blood Pressure and Incidence of Hypertension

It has been shown in more or less random collections of individuals and in groups of patients that obesity is statistically associated with overaverage blood pressure levels (Dublin, Fisk and Kopf, 1925; Huber, 1927; Hartman and Ghrist, 1929; Nuzum and Elliott, 1931; Kirk, 1931, Short and *Johnson*, 1939, Robinson, Brucer and Mass [illegible]

[illegible] the obesity of Cushing's Syndrome and in cortical hyperadrenia. Underaverage *body weight* is associated with underaverage levels of the blood pressure (Symonds, [illegible]

of [illegible]

re[illegible]

ess [illegible]

19[illegible], Terry, 1923; Dublin, Fisk and Kopf [illegible] the obese (Symonds, and [illegible]

1931 [illegible]

Mass [illegible] Moschcowitz, 1945; Adlersberg, Coler and Laval, 1946, Bechgaard, 1946).

There is [illegible]

are to [illegible]

betwe[illegible]

1924, [illegible]

[illegible] twins (Weitz, 1923; *Hines, 1937*; Klemola, 1938).

pressure of most individuals rises with age. There is, however, no certainty that the rises are physiological and we cannot draw the conclusion from our population survey that the rise is gradual over the years.

A further survey was made (Fig. III 5) of 49 hospital inpatients of various ages who had had several blood pressure measurements spread over 15 or more years. It will be seen that the blood pressure of an individual usually rises in 15 years, but there are many exceptions. The mean blood pressures of this hospital series rise with age in much the same way as in other surveys, but the blood pressures of individual patients are often a long way from the mean. Hypertension may develop gradually or become established within a few years.

## THE RELATIONSHIP BETWEEN BLOOD PRESSURE LEVEL, OBESITY, WEIGHT, HEIGHT, AND BUILD

### Obesity in Relation to Body Weight

Many observations have been published relating obesity to blood pressure levels and to the incidence of high blood pressure. In almost all studies of obesity the body weight, or the body weight related to the height, has been used as an index of obesity. Corrections may be made for the effects of increased arm girth. In crude statistics there is an important correlation between body weight, level of blood pressure and the incidence of hypertension. Observations have been made also on body build. The circumference of the chest above nipple level in men (or a little higher to avoid breast tissue in women) divided by the height, has been used as an index of body build by Robinson and Brucer (1940). The authors describe the following body build types:-

Linear build = Chest: height ratio less than 0.50
Linear intermediate build = Chest: height ratio between 0.50 and 0.54
Lateral intermediate build = Chest: height ratio between 0.55 and 0.59
Lateral build = Chest: height ratio 0.60 and over.

There is a strong statistical correlation between overweight and lateral build on the one hand and between underweight and linear build on the other. It follows, therefore, that a series of persons selected for overaverage weight will contain an overaverage proportion of persons of lateral build, and groups selected for underweight will contain more persons of linear build. Under these circumstances it could happen that a statistical correlation established in the first place between blood pressure levels and body weight might in fact be dependent on a relationship between body build and body weight. In order to decide whether body build and body weight have separate effects upon the blood pressure level and the incidence of hypertension, it becomes

necessary to study the effect of overweight and underweight in persons of the same body build. A corresponding difficulty arises in connection with study of the relationship between height and blood pressure. Among tall people there are a larger proportion of persons of linear build and among short people a larger proportion of persons with lateral build Hence it follows that in considering the relationship between height and blood pressure it is desirable to study the effects of height within a uniform body build group. That is to say, to study the blood pressure level and incidence of hypertension among short persons as compared with tall persons, first in a group of persons of lateral build and second in a group with linear build.

It will be seen from what follows that there is much information concerning body weight and hypertension but in only a few of these has a study been made separately of the effects of body weight and body build.

## Effect of Obesity on Blood Pressure and Incidence of Hypertension

It has been shown in more or less random collections of individuals and in groups of patients that obesity is statistically associated with overaverage blood pressure levels (Dublin, Fisk and Kopf, 1925; Huber, 1927, Hartman and Ghrist, 1929; Nuzum and Elliott, 1931; Kirk, 1931; Short and Johnson, 1939; Robinson, Brucer and Mass, 1940, Adlersberg, Coler and Laval, 1946; Boynton and Todd, 1948). This relationship is found not only in the more common forms of obesity but also, as is well known, in the obesity of Cushing's Syndrome and in cortical hyperadrenia. Underaverage body weight is associated with underaverage levels of the blood pressure (Symonds, 1923; [illegible]
1927; Robinson [illegible]
of overav[illegible]
reported [illegible]
essenti[illegible]
1923, [illegible]
and O[illegible]
1931; [illegible]
Mass, [illegible], 1940, Moschcowitz, 1945; Adlersberg, Coler and Laval, 1946, Bechgaard, 1946).

There is good evidence that both essential hypertension and obesity are to some extent genetically determined although the relationship between them is scarcely understood (O'Hare [illegible]
1924; [illegible]

The relationship of obesity to hypertension however is not purely genetic for loss and gain of weight induced by altered food intake have been shown to be associated with fall and rise of blood pressure. This relationship between alteration in body weight and corresponding alteration of blood pressure has been observed in the obese and in persons of normal weight; in normotensives (Benedict, 1915; Benedict, Miles, Roth and Smith, 1919; Preble, 1923; Bauman, 1928; Master and Oppenheimer, 1929; Moschcowitz, 1945); and in hypertensives (Preble, 1923; Rose, 1923; Terry, 1923; Master and Oppenheimer, 1929; Møller, 1931; Moschcowitz, 1945; Fletcher, 1954).

Dublin (1953) on the basis of Metropolitan Life Insurance statistics, confirms the important relationship between overweight and hypertension. He reported that in 2,300 people who reduced their body weight to within the weight limit for standard insurance, the mortality experience was very much superior to the experience in those who had not done so.

Dublin quotes Ley (1939), who analysed the blood pressure findings at the beginning and end of a five year period among nearly 3,000 obese persons. He found that those who reduced their weight by 5 % or more, showed a decline in the averages of the systolic and diastolic pressures, whereas other cases showed an increase. The degree of change in the weight corresponded to the degree of change in the blood pressure.

The magnitude of the blood pressure changes associated with obesity are not easy to state because much depends on the manner of collecting the data, but the blood pressure fall corresponding to an average reduction of 24 pounds was about 32 mm systolic and 16 mm. diastolic in the 72 per cent of obese hypertensives in the series of Adlersberg, Coler and Laval (1946), who had a fall of blood pressure. The difference in the average blood pressure between more or less unselected groups of overweight and underweight individuals is about 10 mm. systolic and 8 mm. diastolic. The effect of obesity is more obvious, however, when the comparison is made between the percentage of hypertensives encountered in individuals who are over the normal standard weight as compared with the percentage among subjects who are under the normal standard weight. The effect of arm girth on blood pressure measurements is discussed in Chapter II.

" In normal dogs and in dogs rendered hypertensive by the Goldblatt method, Wood and Cash (1939) showed that gains and losses of weight were associated with rises and falls of blood pressure, notably of the systolic pressure. The effect of overweight on the blood pressure level in man seems to be more pronounced after the age of 40 and this corresponds to the time of life when the incidence of essential hypertension rises."

### Effect of Body Build on Blood Pressure and Incidence of Hypertension

Larimore (1923) refers to variations in the blood pressure of a group of 417 factory workers, classified according to the bodily habitus. The average blood pressures both in males and females were lower in those of the asthenic type than in the sthenic. Larimore did not take account in this investigation of the relationship between body type and weight. Apparently he relied upon general impressions of bodily habitus for allocating the workers into the different groups.

Robinson and Brucer (1940) provide evidence that linear build is correlated with underaverage body weight and lateral build with overaverage body weight. It becomes of interest to know, therefore, whether body weight or body build is responsible for the observed relationship or whether both play some part.

[illegible] constant, overweight shows a much less significant correlation with the blood pressure than does the build correlation. They have concluded that body build is much more important than weight in determining the predisposition of an individual to high blood pressure. It is of interest in this connection that Diehl and Sutherland (1925) found no relationship between persistent hypertension and vital capacity in student groups.

### Effect of Height on the Blood Pressure

There seems to be little doubt that crude statistics relating height to blood pressure show either no correlation or very little correlation (Alvarez and Stanley, 1930; Reed and Love, 1932).

Robinson (1941) concurs in this finding but points out that the crude statistics are [illegible] a larger proportion [illegible] short [illegible] pressure levels will be increased thereby. Robinson, therefore, subdivides his population of 2,552 men and 2,021 women into groups of comparable body build (girth/height). When, among individuals of the same body build, he examines the effect of height on the blood pressure level, he finds that the taller members of a group have higher blood pressures and the shorter members have lower blood pressures.

### Summary

It would appear that lateral build is associated with a tendency to overweight and linear build with a tendency to underweight. Tallness is associated with linearity and shortness with lateral build. More work is needed on the effect of body build on blood pressure. Changes in body weight are associated with changes in blood pressure level as taken by cuff methods, such that increase in body weight is associated with increase in blood pressure and lowered body weight with lower blood pressure. A part of the rise in blood pressure readings in obesity is due to overestimation of the blood pressure when the arm is obese, but there is evidence of a positive correlation between body weight and blood pressure which does not depend on errors of measurement. Although the matter cannot be settled at the present time, the available information suggests that both body build and body weight are important.

It seems to the author that there are many reasons for regarding the relationships between physical dimensions and blood pressure as important. The topic is related to such problems as the influences of race, geographical environment, and heredity upon blood pressure levels and upon the incidence of hypertension. Many cases of inherited hypertension may, for example, be determined by factors which are strongly correlated with body build or other physical characteristics.

While there is no reason to doubt the importance of body weight in relation to blood pressure level, it is well to point out that many reports of falls of blood pressure with weight reduction are based on simple comparisons of blood pressure measurements before and after a period of treatment. Part of the fall in blood pressure under such conditions is due, almost certainly, to lessened emotional tension as the patients get used to the clinic and its staff.

## EFFECT OF HEREDITY

The predisposition to high blood pressure is often inherited. Exact studies are difficult for it may be necessary to rely for evidence of ancestral hypertension upon a history of stroke or heart failure, and the children at the time of the investigation may not have reached an age at which hypertension is likely to develop. Even so, the evidence is strong.

O'Hare, Walker and Vickers (1924) found family histories suggestive of hypertension among 68 per cent of hypertensive patients and only among 37.5 per cent of controls. Ayman (1934) studied the inheritance of blood pressure among 1,524 members of 227 families. He found that where both parents were fully normotensive the incidence of elevated blood pressure in the children was 3.1 per cent; where one parent was hypertensive 28.3 per cent of children had hypertension;

and where both parents were hypertensive 45.5 per cent of children had hypertension. The children were aged 14 to 39 inclusive. A higher percentage of these children may be expected to exhibit hypertension at a later age. It is of interest that Adson (1941) finds that in hypertensive families the later generations have more severe hypertension.

The possibility that tests may be devised which will reveal a latent predisposition to hypertension is of importance.* Hines (1937) states that a family history of hypertension is five times as frequent among individuals who have hypertension or are hyperreactive to the cold pressor test. He found similar responses in identical twins.* Of subsequent publications some have supported and others failed to confirm the findings of Hines.

Thus, Feldt and Wenstrand (1942), on the basis of 350 subjects, find no statistically significant relationship. Chesley and Chesley (1939) in a study of [illegible] Dieckman and Michel (1935) on 101 [illegible] firm Hines' con- [illegible] correlated with increased response to the cold p[illegible]

It is the author's impression that some of the differences of opinion about the effects on blood pressure of the cold pressor test depend upon the extent to which the blood pressure is allowed to fall towards near-basal levels before application of the stimulus.

Roberts (1940) states that direct transmission through three generations in the absence of marriage of blood relations is practically proof of dominant heredity. There appears to be good evidence in the literature of direct transmission through three generations (Allbutt, 1915, Rosenbloom, 1922, Weitz, 1923; Ayman, 1933).

Platt (1947) made an important contribution by careful separation of his essential (and malignant) hypertension patients from various secondary hypertensive cases. He finds that 59.0 per cent of essential hypertension patients gave a convincing history of hypertension in one or both parents, but such a history was obtained in only 21.1 per cent of other hypertensives. In his normotensive controls 22.5 per cent had a strong history of hypertension in one or both parents, and 25 5 per cent where the controls studied were over 40 years of age.

Of Platt's essential hypertension cases only 6.4 per cent had a history which was strongly against the existence of hypertensive disease in either parent Among other hypertensives 42.1 per cent gave a history against hypertension in either parent, and there were 39 4 per cent with negative parental histories in the control series, and 34 6 per cent in the controls over 40 years. Platt states that a strongly suggestive family history provides nearly a six to one chance that the case is essential hypertension, but where the history is against hypertension in either parent the chances are over three to one in

favour of some other causes for the hypertension. Among Platt's cases 75.4 per cent of his benign hypertensives and 76.5 per cent of his malignant hypertensions exhibited some hereditary tendency. He concludes that the evidence is compatible with the hypothesis that essential hypertension is a hereditary disease conveyed as a Mendelian dominant with a rate of expression of more than 90 per cent. There is some evidence that the rate of expression in any community depends on living conditions, and the degree or intensity of expression may also depend on the environment.

Thomas and Cohen (1955) conducted a detailed investigation of the prevalence of hypertension among the relatives of 266 Johns Hopkins medical students. It was found that hypertension was three times as frequent among siblings of hypertensive individuals as among siblings of normotensive individuals. Søbye (1948) studied the relatives of 186 patients with hypertension. His propositi had to have a systolic blood pressure of 160 mm. Hg or more and simultaneously a diastolic pressure of 100 mm. Hg and proteinuria from traces to 3 parts per 1000. They had not to have any disorder leading to secondary hypertension such as nephritis or a urological condition. Cases of nephrosclerosis (mostly malignant hypertension) were included. Søbye found strong evidence that essential hypertension is inherited but with less than 100 per cent expression of the disorder. He thought the inheritance to be of a Mendelian dominant type. He found essential hypertension and nephrosclerosis to be genetically identical disorders.

Hamilton et al. (1954b) showed that there was an increase in the incidence of hypertension among relatives of hypertensives as compared with normal controls.

They objected to analyses which depended upon choosing some arbitrary level of the blood pressure, and calling patients above the level hypertensive and below it normotensive. Hypertension is, as they point out, a disorder which must be expressed quantitatively. They come to the conclusion that the inheritance is not of a Mendelian dominant type, but is on the same basis as the general resemblance in height or features of parents and offspring. This conclusion seems likely to me for another reason. The blood pressure level is influenced by many factors and it is unlikely that they are all affected by heredity in the same way. In any case the casual blood pressure is the sum of two variables (the basal and supplemental pressures) which would need to be considered separately.

Comparatively few blood pressure measurements in like twins have been reported. A summary of the data available to the author is made in Fig. III 6, where it is seen that there is usually a close relationship between their casual blood pressures.

Verschuer and Zipperlen (1922) studied 112 uniovular and 82 binovular twins. They found the average difference between the

systolic pressures of like twins was 5.1 and between unlike twins was 8.4 mm. Hg. Torsten Lund (1933) reported similar blood pressures in a set of identical girl triplets.

Maxwell and Maxwell (1955) have reported that there is no association between the inheritance of essential hypertension and ABO blood group inheritance.

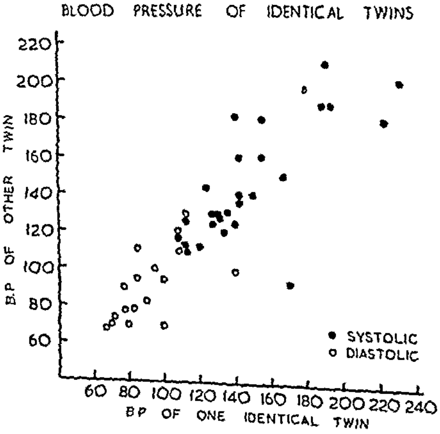



Fig. 111 b

de
Ka
Kl
Watson, 1934, Weitz, 1924) ... Seel, 1939, Wakefield and Dellinger, 1935,

fa
pr ... usually evident before the third month. The blood pressure readings of over 145 mm. are frequent and levels of over 180 mm. have been recorded.

## RACIAL, GEOGRAPHICAL AND ENVIRONMENTAL INFLUENCES ON BLOOD PRESSURE LEVELS

The blood pressure levels of Western European and North American white people have been referred to in the previous section. Among certain Indian, Chinese, African, Phillipine and American Indian peoples the blood pressures are usually lower than those of Europeans and Americans. The differences between the average blood pressures of such groups may be 10 to 20 mm. systolic and 8 to 15 mm. diastolic for comparable ages. This pressure difference is not great but it seems to be associated with considerable difference in the liability of the members of the community to essential hypertension. While it seems probable that race influences the liability to essential hypertension (Kirk, 1931; Shattuck, 1933; Flaxman, 1934; Kean, 1941), there is good evidence that environment has a strong influence upon the predisposition to essential hypertension; and this predisposition seems to be closely related to the levels of the blood pressures encountered in the populations under consideration. Where the average or the modal blood pressure of the population is low it is usually found that the incidence of essential hypertension is low and vice versa (Smirk, 1949). The separate effects of such environmental factors as diet, temperature and physical and emotional stress have not been studied adequately.

Much of the literature concerning the ecology of hypertension is not easily accessible; and for that reason, as well as its importance to those with special interests in the subject, the author has included detail which many readers will find unnecessary. Attention is therefore directed to the mean blood pressures of Chinese and certain other racial groups in Fig. III 7 and to the comment at the end of the section.

### Chinese

China appears to have provided an environment favouring lower blood pressures and there seems to have been a low incidence of essential hypertension. North America and Great Britain favour higher ranges of blood pressure and there is much essential hypertension Evidence that the blood pressure of Chinese in China falls below the level of pressure in Canadian and United States citizens resident in their own countries (Fig. III 7) may be obtained by perusal of papers by Cadbury (1922, 1923), Kilborn (1926), Ying (1926), Foster (1927), Tung (1927, 1928, 1930) and Ride (1938).

Trimble, Whyte and Boyd were cited by Cadbury (1922) as finding the average systolic pressure of Chinese between 18 and 43 years as 100 mm. and the average diastolic 61 mm. The incidence of essential hypertension in much of China is also low (Cadbury, 1922, 1923;

Cruickshank, 1923; Kilborn, 1926; Foster, 1927, 1930); even among well fed sections of the community (Houston, 1929).

Dieuaide (1940) studied 50,000 Chinese patients in Peking and found 1.4 per cent of raised blood pressure. He found 2.8 per cent of

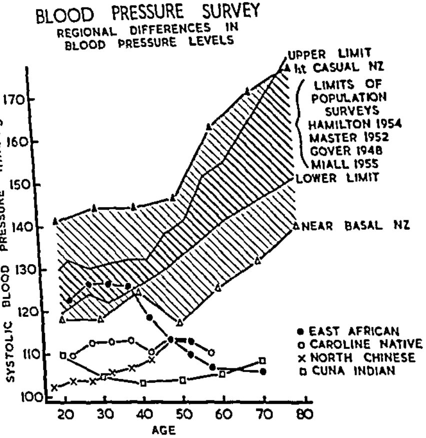



Fig III 7

raised blood pressure in 7,800 non-Chinese people. The hypertension was associated with obesity in 40 per cent of cases and with diabetes in 17 per cent It has been shown by Krakower (1933—34) that the level of the blood pressure of Chinese resident for many years in Canada

is about the same as that of other Canadian residents and essential hypertension occurred quite frequently among them.

Ling (1936), however, in making a statistical study of Chinese life insurance applicants in China found that there was a low mean blood pressure which, however, was associated with the presence of some hypertensives. Ling remarked on the lower body weight of Chinese as compared with North Americans of the same age. He found 21.8 per cent of hypertension in those who were overweight and only 0.1 per cent in those who were underweight Ling, working on life insurance applicants in China, was probably studying a group of comparatively well-to-do people.

An excellent review of the literature on the blood pressures of Chinese has been prepared by Lowenstein (1954). He reexamined certain statistics on Chinese and Americans which he considered to be reasonably comparable and notes much lower blood pressures in the Chinese students. Such errors as he points out would, if corrected, tend to emphasize the differences already reported.

Tung (1928) found that 30 Chinese who had been resident in the United States had falls of pressure on returning to Peking. Americans resident in Peking are said to have lower blood pressures than Americans in America. The evidence on this is provided by Tung (1927) on 58 Americans who experienced a distinct fall of blood pressure on taking up residence in China, and Foster (1927) found the population of 120 Americans in Hunan had an average pressure close to that of the local Chinese population.

The general impression is that most Chinese living in China are lighter in weight and shorter than British and Americans living in their own land and tend to have lower blood pressures and less hypertension. This applies in particular to poor Chinese who may be undernourished, badly housed and sometimes infested with parasites but the difference is present even when living conditions are good. There is some evidence that Chinese migrating to North America acquire higher blood pressures, and Americans who move to China get lower pressures.

### Japanese

Hashimoto et al. (1933) state that essential hypertension is almost as frequent in urban Japanese as in Americans; they find the incidence of hypertension greater in the town than in the country.

Itahara et al. (1955) described a very high incidence of hypertension and apoplexy in Japanese agrarian villages in the basin of the River Omono in Akita prefecture. Indeed, they consider this Akita mortality from cerebral haemorrhage to be the highest in the world and the incidence of hypertension in the population was 30 %. In contrast some secluded fishing villages on the Pacific shore in Iwate prefecture have

the lowest incidence of cerebral haemorrhage in Japan. They refer to the colder climate, greater salt and rice consumption and more inbreeding in Akita as contrasted with Iwate.

Japan has a cold climate in the north and a warm one in the south. The incidence of hypertension in persons over 20 in four cities was:

| | |
|---|---|
| Hachinohe (North) | 9.4 % |
| Sendai | 5.3 % |
| Wakayama | 2.7 % |
| Kagoshima (South) | 1.4 % |

## Negroes

Certain groups of African Negroes have lower blood pressures than those of their race who live in America (Donnison, 1929) and the incidence of high blood pressure is low among some groups of Negroes in Africa (Shattuck, 1930; Heimann, Strachan and Heyman, 1929; Schulze and Schwab, 1936; these last authors also quote personal communications from Taylor, Odaley, Dry and Wakeford). Unfortunately most of the studies of blood pressure levels come from East Africa and recently from South Africa whereas most American Negroes came from West Africa. The report of Odaley concerns the Gold Coast and Shattuck (1930) worked in Liberia and found less hypertension in Liberian Negroes than in American Whites.

Of interest in Donnison's studies is the observation that in his Kenya natives the blood pressure is not very different from that of Europeans living in Europe or America up to the age of 40 but after this the blood pressure level, instead of rising tends to fall away, so that the blood pressure level is actually less after the age of 40 than it is before that age (Fig. III 7).

Jex-Blake (1934) reported on 1,100 post mortems in Kenya; he saw one case of cerebral haemorrhage, apparently the result of syphilis. Vint (1937) says that he has not seen a case of essential hypertension among natives in Kenya, nor do the medical records of the colony show evidence of its occurrence. Krober (1933) also considers high blood pressure to be rare in East Africa.

Williams (1944) states that such cases of hypertension and hypertensive heart disease as occur in [illegible]

[illegible] for the low blood pressures as the prevalence of anaemia, malaria, gonorrhoea, hookworm and yaws as well as spare body build. [illegible]

[illegible] in the overall [illegible] blood pressure which is seen in *middle* and later life in

American and European population groups, even when frank hypertensives are excluded.

Hypertension, however, has a high incidence among Negroes in America. American Negroes after the age of 20 have somewhat higher blood pressures than American Whites (Alvarez and Stanley, 1930; Adams, 1932) and the incidence of high blood pressure is even greater among Negroes than among White residents of the United States (Holmes, 1931; Kirk, 1931; Alvarez and Stanley, 1930; Stone and Vanzant, 1927; Laws, 1932--33; Donnison, 1929; Hedley, 1941; Weiss and Prusmack, 1938; Allen 1931; Flaxman, 1934; Adams, 1932). Temporary hypertension, of a few days duration, following exposure to explosive blast was decidedly more common in Negroes than Whites (Ruskin, Beard and Schaffer, 1948).

Saunders and Bancroft (1942) studied the blood pressure levels in Negroes and Whites living in the Virgin Islands of the United States. The diet was in general, inadequate though sufficient to maintain nutrition. The authors felt that the inhabitants were not much troubled by the stress of modern civilization and were on the whole contented and carefree. They found that among the Negroes there was both more low blood pressure and more high blood pressure than among the Whites. The mean level rose with age from 120 mm. between 15 and 19 years to 164 mm. between 65 and 69 years in males. In females the peak was 184 mm. between 70 and 75 years.

Not all Africans living in Africa have low blood pressures. There appears to be an important incidence of high blood pressure in the South African Bantu and average blood pressures are at European and North American levels.

Ordman (1948) studied 708 male and 814 female Bantu subjects and found a high proportion of hypertensives among males and females of advancing years. The average weight of the hypertensive subjects was greater than that of the normotensives. He did not find any relationship between the heights of the blood pressure and exposure to rural or to urban environments, The Bantu, even in communities scarcely affected by western civilization exhibit blood pressures at European levels and an appreciable incidence of hypertension. Uys (1956), however, finds hypertensive nephrosclerosis less common in the Bantu than in Whites, but when it occurs it is of a more explosive kind and with a higher incidence of malignant nephrosclerosis and uraemic death.

Kesilman (1941), found that in prison inmates hypertension was 3.1 times as common in the Negro as in the White male in every age group. He found that in the age group 30 to 39 hypertension was 6.2 times as frequent, despite malnutrition and tuberculosis. He attributed this to emotional forces brought about by the stress of civilization and

to some basic inherent tendency in Negroes which renders them more liable to the effects of prolonged physical labour.

"There is a tendency to ascribe hypertension in Africans to the impact of civilization. It is of interest, therefore, to note that Dubois (1932) found quite high blood pressure levels in a primitive village in the Belgium Congo. Young people had levels comparable with European standards and the blood pressure rose with age, so that the systolic pressure exceeded 150 mm. Hg in 43 per cent of natives over 40 years.

"There seems little doubt that even in their primitive state some African Negroes may have hypertension and others, notably East Africans, may have little hypertension. There is a general impression that environmental conditions have an important influence on the [illegible] incidence of hypertension. Groups [illegible] western [illegible] pressures [illegible] and an [illegible] g in East [illegible] ion. Much more information is needed about West Africans living in Africa."

## Indians

The situation in regard to essential hypertension in India is complicated by great differences in the way of life of various sections of the community and the available information is scanty. Among the poorer classes in Bengal blood pressures, on the whole, are lower (McCay, 1907) In Bombay essential hypertension is less common than in Anglo-Saxon lands (Raghaven, 1941). Among students resident in London, Indians have lower blood pressures than Anglo-Saxons (Stocks and Karn, 1924). The period of residence in Britain may perhaps have been insufficient to elevate the blood pressure level.

Munroe (1949) studied Indians in the Royal Air Force in India and found that they had a lower mean blood pressure than British under the same circumstances. They were, however, much lighter in weight. It is of interest that insurance applicants in India were reported as having mean blood pressures which were comparable to the figures for the United States (Chopra, Chopra and Chopra, 1942; and Crusetjis and Crusetjis). The United States figures used by Chopra et al. were lower than those of Masters. The living standard of life insurance applicants may be assumed to be, as an average, much higher than that of the general population. I have been informed by many competent clinicians that hypertension in India is by no means uncommon among the more prosperous Indians, especially when there is obesity, and is uncommon among poor Indians.

Schroeder (1953) cites statements from local physicians in Srinagar, Lahore, Calcutta and Colombo to the effect that essential hypertension is rare. The figures were derived from hospital sources.

## American Indians

The South American Indians of Yucatan have low blood pressures and a low incidence of essential hypertension (Shattuck, 1953). Saunders (1933) studied 1066 Mayo Indians, mestizos and mestizas in Yucatan and found the average blood pressure was 4 to 8 mm. below the standards for the United States of America, being about 110 to 119 for Yucatecans as against 120 to 129 for the United States. Among the Yucatecans there were 3 per cent with systolic blood pressures over 160 mm. and 6 per cent over 150 mm Three hundred and ninety-five of his series were over 40 years. He attributed the difference in the blood pressure level to unhurried life and the tropical climate.

The Cuna Indians, living relatively isolated on the San Blas Islands off the coast of Panama, had an average pressure of 106/69 for 407 adults and no case of hypertension was discovered among them (Kean, 1944). They were a healthy people, and even in 48 of them above the age of 55, the mean pressure was under 109/67 (Fig. III 7). The Zuni Indians of New Mexico have low blood pressures and Fleming (1924) reported that hypertension was rare among them.

Stamp and Faught (Cited by Cadbury, 1922) found that the blood pressures of American Indians and American Whites were similar in the early years of life but the blood pressures of American Indians tend to be reduced at about the age of 45 years.

Cohen (1953) found hypertension to be uncommon among the American Indians of Southwestern United States. Among 1,140 hospital admissions he found 1.2 per cent of hypertension (diastolic over 90 mm.), and 0.96 per cent when cases of secondary hypertension were excluded. Cohen cites Salsbury's statement that he found only 4 cases of hypertension among 4,826 Navajos Indians admitted to an Arizona mission hospital.

Chávez (1942) of Mexico found that hypertension accounted for 2.6 per cent of cardiac cases in hospital and 18.4 per cent in private cases. Hospital admissions included more people of Indian extraction and there were more mestizos and whites among the private cases.

Alvarez and Stanley (1930) remark that in Mexican prisoners as compared with United States Whites and Negroes there is much less tendency for the blood pressure to rise with advancing age

Rotta and Miranda (1949) examined 1,878 inhabitants, ages 18 to 71, in Morococha, Peru at a height of 13,850 feet. There were several races with a predominance of Indians. Blood pressures of Indians and

non-Indians did not differ greatly and the means were 108 mm. systolic and 88 mm. diastolic. They found no hypertension.

Shattuck (1938) found relatively low blood pressures among the Indians of the Republic of Guatemala.

### Residents of Panama

A remarkable situation exists in Panama where, according to Marvin and Smith (1942), as many as 94.1 per cent of Panamanians and 83 3 per cent of West Indians (Negroes) had abnormal urine. Practically all Panamanians appeared to have some kind of renal damage. The incidence of hypertension was very much higher in the Negroes. Taylor (1945) reports a much higher level of the blood pressure among Negroes than among Panamanians of Indian extraction. The incidence of hypertension was also higher there among the Negroes than among the Whites. Bays and Scrimshaw (1953) have the impression that the difference in the incidence of hypertension between Negroes and Panamanians is in part of racial origin, even when a correction is made for body weight. Kean (1941) gave the average blood pressure of Panamanians (mainly American Indian extraction) as 106/75 and of West Indians (Negro extraction) as 119/82. Among West Indians he found 9.8 per cent of males had a systolic blood pressure over 150 mm. and only 1.3 per cent of Panamanians attained such levels.

### Australian Aboriginals

Hicks (Personal communication) found that a systolic blood pressure of 110 was the most common in young Australian aboriginals, and in a consecutive series of 120 aboriginals between the ages of 60 and 65 blood pressures higher than 130 systolic were not found. Benign hypertension [illegible]

Nye (1937) reported rather higher average blood pressures than were recorded by Hicks but they found no hypertension in a group of aged aboriginals living in a primitive state. These aboriginals were almost entirely carnivorous but they tended to gorge when hunting was successful and fast often for several days if food was scarce.

### Various

Egyptians on the whole have lower blood pressures than Anglo-Saxon peoples and a somewhat lower incidence of essential hypertension (Ismail, 1928; Smirk, Unpublished). This disorder is, however, by no means uncommon in Egypt (Ismail, 1928). British residents in Egypt have slightly lower blood pressures than the average in Great Britain (Smirk, Unpublished)

The blood pressures in Filipinos and in natives of Puerto Rico seem to be lower than American standards (Ashford and Dowling, 1929, Torgerson, 1929; Salcedo and Pascual, 1932; Lantin, 1933; Concepción and Bulatao, 1916) and the incidence of essential hypertension is probably less (Ashford and Dowling, 1929; Torgerson, 1929; Lantin, 1933); *here I am giving my own interpretation of the authors' figures.* The study of hospital populations by Suárez (1950) show that hypertension is by no means uncommon in Puerto Rico though probably less among poor patients, 3.0—10.0 per cent, than in the United States of America. Among well-to-do patients it may be 10—13 per cent or more.

Murrill (1949) found that there was a high incidence of sub-normal blood pressures in the natives of Ponape Island of the Eastern Carolines (Fig. III 7). The mean systolic blood pressure for males between 20 and 59 was found to be 111.9 mm. and the diastolic, 76.4 mm., and in 124 females from 18 to 59 the systolic pressure was 111.0 mm. and the diastolic 76.6 mm. Surveying their figures it seems that of 39 males of 45 years or more only one subject had a blood pressure as high as 136/100. Among 30 females of 45 years or more the highest blood pressure was 160 systolic. There were in all 3 females with blood pressures of 140 or more. The highest diastolic blood pressure was 102 and there were 3 females with diastolic blood pressures exceeding 100. It appears that the incidence of hypertension is low and may perhaps be associated with the somewhat low level of the blood pressure in the population as a whole. Murrill noted that there was practically 100 per cent infestation with hookworm and that many were suffering from tuberculosis. It may well be that hookworm has some influence upon the average level of the blood pressure. It would be of great interest to know whether such a disorder, if prevalent among the population and perhaps responsible for reducing the average level of the blood pressure, might be responsible also for reducing the incidence of hypertension in the community.

Alexander (1949) found the blood pressure level in the Aleutian Islands approximately the same among young people as in United States of America.

## Comment on the Effect of Race and Environment on Blood Pressure Levels

It is hard to disentangle the factors which cause differences of the blood pressure levels in different parts of the world, but certain facts emerge. Since heredity influences blood pressure levels strongly, it is rather probable that some races may be predisposed to high and other races to low blood pressure levels. The strong positive relationship between linear body build, low body weight and low blood pressure is probably in part genetic and may in part explain the lower blood pres-

sures encountered in American Indians, in Indians and in Chinese. To a certain extent body build is a racial characteristic. Liberal food intake, with gain in weight, may contribute to the much higher incidence of essential hypertension in well-to-do individuals in India and in China. Regional differences in the average blood pressure level are not all racial for in almost all primitive races the incidence of essential hypertension rises in those of the race whose living standards approach those of Europe, North America, Australia or New Zealand. There seems, however, to be some evidence of racial difference, the Negro appears to have appreciably more hypertension than the White when placed under similar conditions and in Panama, American Indians have much less hypertension than Negroes living under conditions which superficially are similar.

Szent-Györgyi (1956) has reported that hypertension is more frequent in American-born than in foreign-born students. After ten years residence in the United States, however, the incidence of hypertension in the foreign-born students was about the same as in American-born.

What has impressed the author[148] most about the data which concern the effect of race, body build, body weight, etc. upon the blood pressure is that, in almost all instances, the factors which lead to a rise in the general level of blood pressure in a population increase also the incidence of high blood pressure, and those things which decrease the general level of the blood pressure also decrease the incidence of hypertension. The possibility arises that long exposure to overaverage blood pressures leads on to further blood pressure elevation and, in predisposed individuals, to sustained hypertension (See Chapter XI).

### The Effects of Tropical Climate

The question of whether a tropical climate leads to lower blood pressure levels or diminished incidence of hypertension in Whites when compared with similar groups resident in U.S.A., Great Britain or the continent of Europe has been much disputed. Several authors [25, 41, 49, 98, 107, 125, 129] claim that the blood pressure is much lower in warm climates Mason (1940) considers that, while there are wide variations, there is a tendency towards somewhat lower blood pressures in warm climates. Other authors [20, 81, 90] state that tropical residence has comparatively little effect on the blood pressure level.

Macpherson (1949) studied 1,000 consecutive subjects in the Royal Australian Air Force serving under tropical conditions in the Bougainville Islands and compared them with 250 [illegible]

[illegible] on 2,000

[illegible] at Long Island, New York. The age groupings of the subjects were comparable. The following figures were obtained:

TABLE III 1.

| | Pulse rate (per min.) | | | Systolic Blood Press. (mm. Hg) | | | Diastolic Blood Press. (mm. Hg) | | | Pulse Pressure (mm. Hg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\bar{x}$ | S | $S\bar{x}$ | $\bar{x}$ | S | $S\bar{x}$ | $\bar{x}$ | S | $S\bar{x}$ | $\bar{x}$ | S | $S\bar{x}$ |
| R.A.A.F. Tropical | 82 90 | 12 10 | 0 382 | 116 50 | 11 25 | 0 365 | 72 09 | 9 44 | 0 293 | 43 73 | 10 92 | 0 345 |
| R.A.A.F. Control | 80 28 | 12 01 | 0 818 | 118 96 | 11 34 | 0 718 | 73.66 | 10 69 | 0 678 | 43 90 | 14 04 | 0 889 |
| American | 74 11 | 10 22 | 0 229 | 117 09 | 9 93 | 0 223 | 71.63 | 8 39 | 0 187 | 47.41 | 9 50 | 0 213 |

$\bar{x}$ = Arithmetic mean. S = Standard deviation. $S\bar{x}$ = Standard deviation of mean

It would appear that there is a very small but significant difference between the tropical and control groups, with a slightly lower pressure in the tropical group. Environmental temperature seems to have no striking effect on the blood pressures of individuals whose sympathetic nervous system is intact. My own observations in Egypt suggest a slight tendency to lower blood pressures in hot weather. Following ganglionic blockade with methonium compounds the sympathetic nervous system is unable to compensate for cutaneous vasodilatation and additional falls of blood pressure occur in hot weather, and patients become aware of this subjectively.

### Effects of Altitude and Anoxia

Cruchet (1925) stated that the blood pressure rises somewhat as altitude is gained, and as altitude falls the pressure falls. Beyner (1932) studied the effect of reducing the pressure in a pressure chamber. He found that as a rule there was a small rise of blood pressure but the blood pressure changes in a aeroplane were larger in degree. He made his measurements with a Pachon oscillometer. With altitude sickness, however, the blood pressure may fall rapidly. Douglas et al. (1913) in their expedition to Pike's Peak, Colorado, found that there were no large changes in blood pressure during a stay at high altitude.

It is of great interest that Gellhorn (1937) found that healthy young men sitting or reclining may breathe 8.5 per cent oxygen for 8 to 10 minutes without important change of blood pressure, but in the erect posture there was a severe fall in blood pressure. Gellhorn and Lambert (1939) find that in the anaesthetized dog in the feet-down position, the carotid artery blood pressure falls more during anoxia than under control conditions. McDowall (1930) states that acapnia diminishes the tone of the vasomotor centre, hence the blood pressure falls. In experiments where anoxia causes respiratory failure the blood pressure falls, but if artificial respiration is given the blood pressure rises.

## References

1 Adams, J. M Some racial differences in blood pressures and morbidity in a group of white and coloured workmen Amer. J. med. Sci, 184. 342, 1932.
2 Adlersberg, D, Coler, A. R, and Laval, J. Effect of weight reduction on course of arterial hypertension J. Mt Sinai Hosp., 12: 984, 1946
3 Adson, A W. The surgical consideration of essential hypertension Univ of Pennsylvania Bicentennial Conference, p 21, 1941. Cited by Daley, R M, Ungerleider, H. E, and Gubner, R. S, J. Amer. med Ass, 121. 383, 1943
4 ... of the Aleutian Islands (1948). New
5 ... luding angina pectoris. Macmillan & Co, London, ... ishberg, A. M, Hypertension and nephritis, Lea and Febiger, Philadelphia, 1954, 5th edn
6 Allen, F P Cardiovascular impairment among one thousand negro factory workers. J. industr. Hyg, 13. 164, 1931.
7 Alvarez, W C, and Stanley, L. L Blood pressure in six thousand prisoners and four hundred prison guards. A statistical analysis Arch intern Med, 46· 17, 1930
8 Ashford, B K, and Dowling, G B A series of blood pressures in 250 cases in Puerto Rico Puerto Rico J. publ Hlth, 5· 477, 1929
9 Ayman, D The hereditary aspect of arteriolar (essential) hypertension· Study of three generations of a family. New Engl. J. Med, 209: 194, 1933
10 Ayman, D Heredity in arteriolar (essential) hypertension: A clinical study of the blood pressure of 1,524 members of 277 families Arch intern Med, 53 792, 1934
11 Barach, J H The constitutional factors in hypertensive disease J Amer. med Ass, 91· 1511, 1928
12 Bauman, L Obesity Recent reports in the literature and results of treatment J Amer med Ass, 90 22, 1928
13 Bays, R P, and Scrimshaw, N. S. Facts and fallacies regarding the blood pressure of different regional and racial groups Circulation (N.Y.), 8· 655, 1953
14 Bechgaard, P Arterial hypertension· Follow-up study of 1000 hypertonics Acta med scand, suppl 172· 3, 1946
15 Benedict, F G A study of prolonged fasting Carnegie Institution of Washington, Washington, D C, 1915
16 Benedict, F G, Miles, W R., Roth, P., and Smith, H M. Human vitality and efficiency under prolonged restricted diet. Carnegie Institution of Washington, Publication No 280, 1919
17 Beyne, J Les variations de la tension artérielle chez l'homme sous l'influence de la pression atmosphérique Médecine, 13: 670, 1932.
18 Bowes, L M Blood pressure in the aged, A study of 150 cases from 65 to 95 years of age J Lab clin Med, 2. 256, 1916
19 Boynton, R E, and Todd, R. L Relation of body weight and family ...
20 ...
21 Briggs, J F, and Oerting, H The prognostic value of cold test in pregnancy Minn Med., 20. 382, 1937

22 BRUNTON, L Blood pressure in man: Its estimation and indications for treatment. Brit. med. J., 2: 64, 1909.
23 CADBURY, W. W. Blood pressure of normal Cantonese students. Arch intern. Med., 30: 362, 1922.
24 CADBURY, W. W. Blood pressure of normal Cantonese Students. Chin med. J., 37: 823, 1923.
25 CHAMBERLAIN, W. P. Philipp. J. Sc. B., 6: 467, 1911. Cited by Cadbury, W W., Arch. intern. Med., 30: 362, 1922.
26 CHÁVEZ, I. The incidence of heart disease in Mexico; a study of 2,400 cases of organic heart disease. Amer. Heart J., 24: 88, 1942.
27 CHESLEY, L C., and CHESLEY, E. R Cold pressor test in pregnancy. Surg Gynec. Obstet., 69: 436, 1939.
28 CHOPRA, R. N., CHOPRA, G. S, and CHOPRA, I. C A study of the normal blood pressure in Indians Indian med Gaz, 77: 21, 1942.
29 COHEN, B. M Arterial hypertension among Indians of the southwestern United States Amer. J. med. Sci, 225: 505, 1953.
30 CONCEPCIÓN, I., and BULATAO, E. Blood pressure picture of the Filipinos Philipp. J. Sci (B), 11: 135, 1916
31 CRUCHET, R. Influence des variations de la pression atmosphérique sur la pression artérielle et le mal des aviateurs Presse méd., 33: 1489, 1925
32 CRUICKSHANK, E W. H The mechanisms of the regulation of the H-ion concentration of the blood. Chin. med. J, 37. 116, 1923
33 CRUSETJIS, J J, and CRUSETJIS, R J J. Cited by Bays, R P, and Scrimshaw, N. S., Circulation (N.Y), 8: 655, 1953
34 DIECKMANN, W. J., and MICHEL, H L Thermal study of vasomotor lability in pregnancy — Preliminary report. Arch. intern Med, 55. 420, 1935.
35 DIEHL, H S., and SUTHERLAND, K H Systolic blood pressures in young men, including a special study of those with hypertension Arch intern Med., 36. 151, 1925
36 DIEUAIDE, F R Observations on hypertension among the Chinese people Bull Johns Hopk. Hosp, 66: 408, 1940
37 DONNISON, C P Blood pressure in African native, bearing upon aetiology of hyperpiesia and arterio-sclerosis Lancet, 1. 6, 1929.
38 DOUGLAS, C G, HALDANE, J S, HENDERSON, Y., and SCHNEIDER, E C VI Physiological observations made on Pike's Peak, Colorado, with special reference to adaptation to low barometric pressures Philos Trans B, 203 262, 1913
39 DOXIADES, L, and UHSE, W Neue klinische Befunde an Zwillingen. Mschr Kinderheilk., 62. 196, 1934
40 DUBLIN, L I Relation of obesity to longevity New Engl. J. Med, 248: 971, 1953
41 DUBLIN, L I, FISK, E L, and KOPF, E W Physical defects as revealed by periodic health examinations. Amer J med Sci., 170. 576, 1925.
42 DUBOIS, A Note sur la tension artérielle chez les indigènes congolais. Ann Soc belge Méd trop., 12 133, 1932
43 FABER, H K A formula expressing a general relationship between blood pressure and body weight Proc. Soc exp. Biol (N Y), 25: 77, 1927.
44 FAUGHT, F. A Blood pressure from the clinical standpoint W B Sanders & Co, Philadelphia, 1916. Cited by Cadbury, W W, Arch. intern Med, 30: 362, 1922
45 FELDT, R. H, and WENSTRAND, D E. W The cold-pressor test in subjects with normal blood pressure. Report of observation on 350

subjects with special reference to the family history. Amer. Heart J., 23 766, 1942.
46 FLAXMAN, N. Heart disease in the Middle West; 1646 cases at a Chicago hospital. Amer J. med. Sci, 188. 637, 1934
47 FLEMING, W. D. Blood chemistry and blood pressure standards. I. The effect of tropical residence on the blood chemistry and the blood pressure J. metab Res, 6 87, 1924.
48 FLETCHER [illegible]
of ot [illegible]
49 FOSTER, [illegible]
40. 39, 1927.
50 FOSTER, J H. The practice of medicine in China and New England with observations on hypertension New Engl J. Med, 203 1073, 1930
51 FOURMAN, L. P R Effect of climate on the blood pressure in acclimatized subjects Trans roy Soc. trop Med. Hyg, 42. 293, 1949
52 FRIEDMAN, M., and KASANIN, J. S. Hypertension in only one of identical twins Report of a case with considerations of psychosomatic factors. Arch intern. Med, 72· 767. 1943
53 FRÖLICH, K. Jugendliche Zwillinge mit arteriellem Hochdruck Med Klin, 33· 1196, 1937.
54 GAGER, L T Hypertension. Williams & Wilkins Co, Baltimore, p. 329, 1930 Cited by Moschcowitz, E., J. Mt Sinai Hosp, 11: 257 1945
55 GE[illegible]
56 GE[illegible]
57 GOULD, A R A survey of blood pressures in West Feliciana Parish. Bull Tulane med Fac, 13 107, 1954
58 GOVER, M Physical impairments of members of low-income farm families — 11,490 persons in 2,477 rural families examined by [illegible]
[illegible]
59 GRAHAM A W., HINES, E A., JR, and GAGE, R. P. Blood pressures in children between ages of 5 and 16 years Amer. J. Dis Child, 69: 203, 1945.
60 HAMILTON, M, PICKERING, G W, FRASER ROBERTS, J. A, and SOWRY, G S C Aetiology of essential hypertension· (1) The arterial pressure in the general population (2) Score for arterial blood pressures adjusted for differences in age and sex. Clin. Sci, 13: 11, 1954a.
61 HAMILTON, M, PICKERING, G W, FRASER ROBERTS, J. A, and SOWRY, G S G The aetiology of essential hypertension (4) The role of inheritance Clin Sci, 13 273, 1954b
62 HARTMAN, H R, and GHRIST, D G Blood pressure and weight. Arch. intern Med, 44 877, 1929
63 HASHIMOTO, H, AKATSUKA, K, TSUJII, I, and SHIRAISHI, H. Incidence of hypertension among urban Japanese. Ann intern. Med, 7. 615, 1933
64 HEDLEY, O F Publ Hlth Bull (Wash), 3· 39, 1941. Cited in Bull. Hyg (Lond), 17 553, 1942
65 HEIMANN, H L, STRACHAN, A S, and HEYMAN, S. C. Cardiac disease among south African Non-Europeans (preliminary note). Brit med. J, 1 344, 1929
66 HICKS, S Personal communication

67 HINES, E. A., JR. Hereditary factor in essential hypertension. Ann. intern. Med., **11**: 593, 1937.

68 HINES, E. A., JR., and PIPER, M. C. Identical twins with essential hypertension and prolapse of the uterus Proc. Mayo Clin., **12**: 815, 1937.

69 *HOLMES, S. J. Differential mortality in the American Negro* Hum. Biol., **3**: 203, 1931.

70 HOLMGREN, I. Studies of arterial tension on 4,864 patients from private practice Acta med. scand., **151**: 237, 1955.

71 HOUSTON, W. R. The spasmogenic aptitude. Med. Clin. N. Amer., **12**. 1285, 1929

72 HUBER, E. G. Systolic blood pressures of healthy adults in relation to body weight. *J. Amer. med. Ass., 88: 1554, 1927.*

73 ISMAIL, ABD-EL-AZIZ. Aetiology of hyperpiesis in Egyptians. Lancet, **2**, 275, 1928.

73a ITAHARA, K., FUKUCHI, S, FUJIBAYASHI, T, and YAMAGUCHI, M Frequency of essential hypertension and the influence of environmental condition thereon. Tohoku J. exper. Med, **61**: 231, 1955

74 JANEWAY, T. C The clinical study of the blood pressure. D. Appleton & Co., New York, p 109, 1904

75 JEX-BLAKE, A. J. High blood pressure. E. Afr. med. J., **10**: 286, 1934.

76 JUDSON, C. F., and NICHOLSON, P. Blood pressure in normal children. Amer J. Dis. Child., **8**: 257, 1914.

77 *KAHLER, O. H, and WEBER, R Zur Erbpathogie von Herz — und Kreislaufferkrankungen:* Untersuchungen an einer auslesefreien Zwillingsserie Z. klin. Med, **137**: 380, 1939

78 KEAN, B H Blood pressure studies on West Indians and Panamanians living on the Isthmus of Panama Arch. intern. Med., **68**: 466, 1941.

79 KEAN, B H. The blood pressure of the Cuna Indians. Amer. J. trop Med, **24** 341, 1944.

80 KESILMAN, M. The incidence of essential hypertension in white and negro males Med. Rec (N.Y), **154**: 16, 1941.

81 KILBORN, L G Blood pressure of Szechwanese students Chin med J, **40**. 1, 1926

82 *KILPATRICK, J A The variation of casual, basal and supplemental blood* pressures in health and in essential hypertension Brit Heart J., **10**: 48, 1948.

83 KIRK, E J Hypertension in industry J industr. Hyg, **13**: 314, 1931

84 KLEMOLA, E Essentielle Hypertonie bei 23 jährigen eineigen Zwillingen. Z menschl Vererb.—u KonstitLehre, **22**: 69, 1938

85 KRAKOWER, A The blood pressure of Chinese living in Eastern Canada Amer Heart J, **9**: 396, 1933—34

86 KRÖBER, F Beobachtungen und Erfahrungen in der ostafrikanischen Praxis Klin Wschr, **18**: 724, 1933

87 LANTIN, G T Blood pressure in aged Filipinos, preliminary report. *J. Philipp med Ass, 13: 191, 1933*

88 LARIMORE, J W A study of blood pressure in relation to types of bodily habitus. Arch intern Med, **31** 567, 1923

89 LAWS, C L. The etiology of heart disease in whites and negroes in Tennessee Amer. Heart J, *8 608, 1932—33*

90 LEMANN, I I The effect of a long continued subtropical summer on high blood pressure Amer J trop Med., **12**: 331, 1932.

91 LEY, H. A Proceedings of the Life Ext Exam, **1** 33, 1939. Cited by Dublin, L I, New Engl J Med, *248 971, 1953*

92 LING, W K. The blood pressure of the Chinese: A statistical study of 20,948 life insurance applicants Chin med. J, **50** 1773, 1936

93 LOWENSTEIN, F. W. Some epidemiological aspects of blood pressure and

94 MCCAY, D. Physiological and pathological observations on Wright's method of testing the blood and urine. Lancet, I: 1483, 1907.
95 MCDOWALL, R. J. S. The effect of carbon dioxide on the circulation. J. Physiol (Lond ), 70. 301, 1930.
96 MACPHERSON, R. K Tropical fatigue. University of Queensland Papers, 1: No. 10, 1949. University of Queensland Press, Brisbane
97 MARVIN, H. P., and SMITH, E. R. Hypertensive cardiovascular disease in

98 MAS

and mouth temperature of 21 English and American women. Amer. J. trop Med, 20. 669, 1940.
99 MASTER, A. M., GARFIELD, C. I., and WALTERS, M. B. Normal blood pressure and hypertension. Lea and Febiger, Philadelphia, 1952.
100 MASTER, A. M., and OPPENHEIMER, E. T. A study of obesity. J. Amer. med. Ass, 92. 1652, 1929
100a MAXWELL, R. D. H., and MAXWELL, K. N. ABO blood groups and hypertension. Brit. med J, 2: 179 1955
101 MIALL, W. E., and OLDHAM, P. D. A study of arterial blood pressure and its inheritance in a sample of the general population. Clin. Sci, 14: 459, 1955
102 MOLLER, E. Results of exclusively dietary treatment in 46 cases of obesity. Acta med. scand, 74: 341, 1931
103 MONROE, R. T. Diseases in old age. Harvard University Press, Cambridge 1951
104 MOSCHCOWITZ, E. Essays on the biology of disease. J. Mt Sinai Hosp, 11. 357, 1945.
105 MUNROE, A. F. Basal metabolic rates and physical fitness scores of British and Indian males in the tropics. J. Physiol. (Lond ), 110: 356, 1949
106 MURRILL, R. I. A blood pressure study of the natives of Ponape Island, Eastern Carolines. Hum. Biol, 21: 47, 1949
107 MUSGRAVE, W. E., and SISON, A. G. Blood pressure in the tropics. Philipp. J. Sci B, 5: 325, 1910. Cited by Cadbury, W. W., Arch. intern. Med, 30. 362, 1922
108 NADOR-NIKITIS, E. Sur l'étiologie de l'hypertension artérielle essentielle et de la sclérose rénale. Arch. mal. Coeur 18.
109 NEEL, H. B.
110 NOZUM, F. R
hyperten
111 NYE, L. J. J. Blood pressure in the Australian aboriginal with a consideration of possible aetiological factors in hyperpiesia and its relation to civilization. Med. J. Aust, 2: 1000, 1937.
112 ODALEY, P. D. Personal communication. Cited by Schulze, P. D., and Schwab, E. A., Amer. Heart J, 11. 66, 1936
113 O'HARE, J. P., WALKER, W. G., and VICKERS, M. C. Heredity and hypertension. J. Amer. med. Ass, 83. 27, 1924
114 ORDMAN, B. A review of the incidence of hypertension in the Non-European races; survey of blood pressures in South African Bantu. Clin. Proc, 7: 183, 1948

115 PAGE, I. H, and CORCORAN, A. C. Arterial hypertension: Its diagnosis and treatment. Year Book Publishers, Chicago, p. 252, 1945
116 PALMER, R. S. Etiologic factors in hypertension. New Engl. J. Med, **205**: 1233, 1931.
117 PLATT, R. Heredity in hypertension Quart. J. Med., n s. *16*: 111, 1947.
118 PREBLE, W. E. Obesity: Observations on one thousand cases. Boston med. surg. J., *188*: 617, 1923.
119 RAGHAVAN, P. Aetiological incidence of heart disease in Bombay — Analysis of 4,335 autopsies. *J. Indian med. Ass., 10: 365, 1941.*
120 REED, L. J., and LOVE, A. G. Biometric studies on U.S. Army officers — somatological norms, correlations and changes with age. Hum. Biol., 4: 509, 1932.
121 REIS, R. A, and CHALOUPKA, A. J. Blood pressure in the new-born following normal and pathological labor. Surg., Gynec, Obstet, 37. 206, 1923.
122 RIDE, L. Genetics and the Clinician. John Wright & Sons Ltd, Bristol p. 98, 1938.
123 ROBERTS, J A. F. An introduction to medical genetics, London, 1940 Cited by Platt, R., Quart J Med, n.s **16**. 111, 1947.
124 ROBINSON, S C. Hypertension in relation to height; variation with body build and obesity. J. Lab. clin Med, *26*: 930, 1941.
125 ROBINSON, S. C., and BRUCER, M. Range of normal pressure; statistical and clinical study of 11,383 persons. Arch. intern. Med., *64*: 409, 1939.
126 ROBINSON, S C, and BRUCER, M Hypertension, body build and obesity. Amer J med Sci, **199** 819, 1940.
127 ROBINSON, S C, BRUCER, M., and MASS, J. Hypertension and obesity; a statistical and clinical study of 10,883 individuals. J Lab clin Med, *25*: 807, 1940
128 RODDIS, L. H, and COOPER, G W The effect of climate on blood pressure J Amer med Ass., *87* 2052, 1926
129 RODRÍGUEZ MOLINA, R, and SUÁREZ, R M Estudio de tensión arterial en Puerto Rico. Bol Asoc Méd Puerto Rico, *22*· 114, 1930
130 RONY, H R. Obesity and leanness Lea and Febiger, Philadelphia, 1940
131 ROSE, R H Weight reduction, its indications in high blood-pressure. Amer Med, **18**· 418, 1923
132 ROSENBLOOM, J Familial hypertension, with report of a case J. Lab clin Med, *8*. *681*, *1922*
133 ROTTA, A, and MIRANDA, A Normal values of the arterial pressure and frequency of arterial hypertension in high altitudes Amer Heart J, **37**· 670, 1949
134 RUCKER, M. P, and CONNELL, J W Blood pressure in the new-born. Amer J. Dis Child, **27**· 6, 1924
135 RUSKIN, A, BEARD, O W, and SCHAFFER, R L Blast hypertension Amer. J. Med, **4**: 228, 1948
136 RUSSEK, H I, and ZOHMAN, B L Normal blood pressure in senescence, A study of 3691 white male subjects between the ages of 60 and 95 years Geriatrics, **1**· 113, 1946
137 SALCEDO, J., JR, and PASCUAL, W Filipino physiologic constants J Philipp med Ass, **12**. 205, 1932
138 SAUNDERS, G M. Blood pressure in Yucatecans Amer J med Sci, **185**· 843, 1933
139 SAUNDERS, G M, and BANCROFT, H Blood pressure studies on Negro and white men and women living in the Virgin Islands of the United States Amer. Heart J, **23** 410, 1942
140 SCHNEIDER, E C, and TRUESDELL, D. A statistical study of the pulse

rate and the arterial blood pressures in recumbency, standing, and after standard exercise. Amer. J. Physiol., 61: 420, 1922

141 SCHROEDER, H A. Hypertensive diseases. Henry Kimpton, London, 1953.

142 SCHULZE, V. E., and SCHWAB, E. H. Arteriolar hypertension in the American Negro Amer. Heart J., 11: 66, 1936

143 SHATTUCK, G C The African Republic of Liberia and the Belgian Congo: Report of the Harvard Expedition to Liberia Harvard University Press, Cambridge, 1930 Cited by Schulze, V. E., and Schwab, E. H. Amer Heart J, 11: 66, 1936

144 SHATTUCK, G. C The Peninsula of Yucatan; Medical, biological, meteorological and sociological studies Carnegie Institution of Washington, Washington D C, 1933

145 SHATTUCK, G C A medical survey of the Republic of Guatemala. Carnegie Institution of Washington, Washington D C, 1938 Cited by Taylor, C E, Amer J Path, 21: 1031, 1945

146 SHORT, J J, and JOHNSON, H J The evaluation of the influence of overweight on blood pressures of healthy men. Amer. J. med. Sci, 198 220, 1939.

147 SMIRK, F H Unpublished observations

148 SMIRK, F H. Pathogenesis of essential hypertension Brit. med. J., 1: 791, 1949

148a SMIRK, F H, and HALL, W H Unpublished, 1956

149 SØBYE, P Heredity in essential [illegible]

150 STAMP, H, and FAUGHT, F A Personal communications Cited by Cadbury W W, Arch intern Med, 30 362, 1922.

151 STOCKS, P, and KARN, M N Blood pressure in early life: A statistical study Cambridge University Press, 1924

152 STONE, C T, and Vanzant, F R Heart disease as seen in southern clinic, clinical and pathological survey J Amer. med. Ass, 89: 1473, 1927

153 SUÁREZ, R M Incidence of hypertension in Puerto Rico Ann intern Med, 33 346, 1950

154 SYMONDS, B The blood pressure of healthy men and women. J. Amer. med Ass, 80 232, 1923

154a SZENT-GYORGYI, N Blood pressure studies among American and foreign-born students Circulation, 14 17, 1956

155 TAYLOR, C E Racial distribution of nephritis and hypertension in Panama Amer J Path, 21 1031, 1945

156 TERRY, A H, JR Obesity and hypertension J Amer med. Ass, 81, 1283, 1923

157 THOMAS, C B, and COHEN, B H The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes Ann intern Med, 42: 90, 1955

158 TORGERSON, W R Blood pressure findings in Porto Rico Porto Rico J publ Hlth, 5 438, 1929.

159 TORSTEN LUND, S E A psycho-biological study of a set of identical girl triplets Hum. Biol, 5 1, 1933

160 TRELOAR, A E Normal blood pressure Arch intern. Med, 66: 848, 1940.

161 TRIMBLE, C G, WHYTE, D, and BOYD, H W Cited by Cadbury, W. W., Arch intern Med., 30: 362, 1922

162 TUNG, C L Relative hypotension of foreigners in China. Arch intern. Med, 40 153, 1927

163 TUNG, C. L. The blood pressure of Chinese in China and in the U.S.A. Chin. J. Physiol. rep. ser., 1: 93, 1928.

164 TUNG, C. L. Blood pressure of Northern Chinese males. Chin. J. Physiol., 4: 117, 1930

164a UYS, C J. The pathology of renal disease in the Bantu on the Witwatersrand — hypertensive vascular disease. S. Afr. J. Lab. Clin. Med., 2: 13, 1956.

165 VEALE, A. M. O., HAMILTON, M., IRVINE, R. O H, and SMIRK, F H. Casual and near basal pressures in a population survey. Proc. Univ. Otago med. Sch., 34: 20, 1956

166 VERSCHUER, O., and ZIPPERLEN, V. Die erb- und umweltbedingte Variabilität der Herzform. (Nach Rontogenfernaufnahmen des Herzens bei Zwillingen). Z. klin Med., 112: 69, 1922.

167 VINT, F. W Post mortem findings in the native of Kenya. E. Afr. med. J., 13: 322, 1937.

168 WAKEFIELD, E. G., and DELLINGER, S C. A report of identical albino twins of negro parents Ann. intern Med., 9: 1149, 1935.

169 WATSON, E. M. Diabetes mellitus in twins Canad med. Ass. J., 31: 61, 1934.

170 WEISS, A. Über den Ruheblutdruck beim Manne zwischen 17 und 60 Jahren. Arch. Kreisl. Forsch., 17. 176, 1951.

171 WEISS, M M, and PRUSMACK, J J. Essential hypertension in the Negro. Amer. J. med Sci, 195: 510, 1938

172 WEITZ, W Zur Aetiologie der genuinen oder vasculären hypertension. Z. klin. Med., 96: 151, 1923.

173 WEITZ, W. Studien an eineigen Zwillingen Z klin Med, 101: 115, 1924.

174 WILLIAMS, A W. Heart disease in the native population of Uganda Part 4 Hypertensive heart disease E Afr med J, 21: 368, 1944

174a WETHERBY, M. A comparison of blood pressure in men and women: A statistical study of 5,540 individuals Ann. intern Med, 6: 754, 1932.

175 WOOD, J. E., JR, and CASH, J R Obesity and hypertension clinical and experimental observations. Ann intern Med, 13. 81, 1939

176 YING, Y Y. Blood pressure of healthy individuls in Shaohing Chin. med. J, 40 641, 1926

## CHAPTER IV

# INFLUENCE OF CHANGES IN LIVING CONDITIONS ON THE BLOOD PRESSURE LEVEL

The basal blood pressure is, by definition, the pressure taken during physical and mental rest and when the metabolism is basal. Most of the rises and falls of the casual blood pressure under daily living conditions represent changes in the supplemental (casual minus basal) blood pressure. The supplemental pressure, ordinarily recorded, represents the response of the circulatory system to the stimulus of a medical interview. It does not follow that the possession of a high or a low supplemental pressure in this one situation is an indication that an individual is likely to have a similar level of the supplemental pressure in another situation. For example, we encounter patients who give large blood pressure rises in emotional situations and small responses to the cold pressor test.

Reference will be made later to evidence that the level of the supplemental component of the casual blood pressure, *as ordinarily determined*, the stimulus being a medical interview, has surprisingly little influence on the patient's outlook [illegible]
*of life*. This statement, however, [illegible]
pressures which represent the res[illegible]
not implied that rises in the supplemental pressures from continued emotional stress, exercise, or other causes, are without effect on the patient's physical health. Indeed, we have just discharged from our hospital a hypertensive patient of magnificent physique, previously unconscious of the least defect in his health, who experienced a stroke during the strain of attempting, unaided, to lift a sack of sand on to a lorry.

It is of great [illegible]
in [illegible]
inf[illegible] interpretation of blood pressure measurements and should be useful knowledge for anyone who has charge of the treatment of hypertensive patients.

### Effect of Emotion and Tenseness

The subject is of considerable importance and is treated in more detail in Chapter VII. Stressful interviews, or causes of emotion or tenseness, elevate the blood pressure to a variable degree. Some persons express emotional overactivity by small and others by considerable blood pressure rises, the large responses being much com-

163 TUNG, C. L. The blood pressure of Chinese in China and in the U.S.A. Chin. J. Physiol rep. ser., 1: 93, 1928.

164 TUNG, C. L. Blood pressure of Northern Chinese males. Chin. J. Physiol., 4: 117, 1930

164a UYS, C J. The pathology of renal disease in the Bantu on the Witwatersrand — hypertensive vascular disease. S. Afr. J. Lab Clin Med, 2: 13, 1956.

165 VEALE, A. M. O, HAMILTON, M., IRVINE, R. O. H, and SMIRK, F. H Casual and near basal pressures in a population survey. Proc. Univ Otago med. Sch., 34: 20, 1956

166 VERSCHUER, O., and ZIPPERLEN, V. Die erb- und umweltbedingte Variabilität der Herzform. (Nach Rontogenfernaufnahmen des Herzens bei Zwillingen). Z. klin Med., 112: 69, 1922.

167 VINT, F. W. Post mortem findings in the native of Kenya. E. Afr. med J., 13: 322, 1937.

168 WAKEFIELD, E. G., and DELLINGER, S C. A report of identical albino twins of negro parents Ann intern Med., 9. 1149, 1935.

169 WATSON, E. M. Diabetes mellitus in twins Canad med Ass J., 31: 61, 1934.

170 WEISS, A. Über den Ruheblutdruck beim Manne zwischen 17 und 60 Jahren. Arch. Kreisl. Forsch, 17: 176, 1951

171 WEISS, M. M, and PRUSMACK, J. J Essential hypertension in the Negro. Amer J med. Sci, 195: 510, 1938

172 WEITZ, W Zur Aetiologie der genuinen oder vasculären hypertension Z. klin. Med, 96: 151, 1923

173 WEITZ, W. Studien an eineiigen Zwillingen Z. klin. Med., 101: 115, 1924.

174 WILLIAMS, A W. Heart disease in the native population of Uganda Part 4 Hypertensive heart disease E Afr med. J., 21: 368, 1944

*174a WETHERBY, M A comparison of blood pressure in men and women:* A statistical study of 5,540 individuals Ann intern Med, 6: 754, 1932.

175 WOOD, J. E., JR, and CASH, J. R. Obesity and hypertension: clinical and experimental observations Ann intern. Med, 13: 81, 1939.

176 YING, Y. Y Blood pressure of healthy individuls in Shaohing Chin med J, 40: 641, 1926

CHAPTER IV

# INFLUENCE OF CHANGES IN LIVING CONDITIONS ON THE BLOOD PRESSURE LEVEL

The basal blood pressure is, by definition, the pressure taken during physical and mental rest and when the metabolism is basal. Most of the rises and falls of the casual blood pressure under daily living conditions represent changes in the supplemental (casual minus basal) blood pressure. The supplemental pressure, ordinarily recorded, represents the response of the circulatory system to the stimulus of a medical interview. It does not follow that the possession of a high or a low supplemental pressure in this one situation is an indication that an individual is likely to have a similar level of the supplemental pressure in another situation. For example, we encounter patients who give large blood pressure rises in emotional situations and small responses to the cold pressor test.

Reference will be made later to evidence that the level of the supplemental component of the casual blood pressure, *as ordinarily determined*, the stimulus being a medical interview, has surprisingly little influence on the patient's outlook as regards health and expectation of life. This statement, however, only applies to those supplemental pressures which represent the responses to medical interviews. It is not implied that rises in the supplemental pressures from continued emotional stress, exercise, or other causes, are without effect on the patient's physical health. Indeed, we have just discharged from our hospital a hypertensive patient of magnificent physique, previously unconscious of the least defect in his health, who experienced a stroke during the strain of attempting, unaided, to lift a sack of sand on to a lorry.

It is of [illegible] in [illegible] [illegible] interpretation of blood pressure measurements and should be useful knowledge for anyone who has charge of the treatment of hypertensive patients

## Effect of Emotion and Tenseness

The subject is of considerable importance and is treated in more detail in Chapter VII. Stressful interviews, or causes of emotion or tenseness, elevate the blood pressure to a variable degree. Some persons express emotional overactivity by small and others by considerable blood pressure rises, the large responses being much com-

moner among essential hypertension patients. Large blood pressure increases may occur when the patient is not conscious of emotion; and it seems likely that mental states of "tenseness", "preparedness" or "alertness" may be associated with blood pressure increases, even when there is no feeling of "alarm". It is sometimes stated that psychosomatic disorders may arise from emotional reactions which do not reach consciousness. In our clinic the impression has been gained that a wide variety of cerebral stimuli may evoke pressor responses, and that many of these mental or emotional reactions are simple and understandable.

In normal and in hypertensive patients whose blood pressures have been reduced to a near basal level by physical and emotional relaxation, a conversation on neutral topics with the examiner may elevate the blood pressure by 5 to 20 mm. systolic, 0 to 10 mm. diastolic. A conversation likely to provoke emotion — such as discussion with a hypertensive patient of the death of a relative from hypertension— is likely to produce much bigger blood pressure rises; often 20/10, sometimes even 70/30 mm. Hg. Ayman (1934) has noted the considerable difference between clinic blood pressures and blood pressures taken at home. We find blood pressures are higher when taken at a busy hypertensive outpatient clinic than when taken by the same person in another and quieter part of the hospital. Repeated measurement of the blood pressures leads to a further blood pressure fall. It has been mentioned already (Chapter III) that significant differences among published statistics of blood pressure levels may depend on very simple differences in the conditions under which the blood pressure was taken, and differences will be found between clinic blood pressures and home blood pressures; blood pressures taken by a strange physician, by a family physician, and by a nurse or technician; between single blood pressures taken at first contact with the patient and single blood pressures taken towards the end of a satisfactory consultation. The lowest of a short series of blood pressures will differ from a single blood pressure; blood pressures taken in a quiet room without apparatus will differ from blood pressures taken close to a table containing medical instruments; blood pressures taken in the morning and blood pressures taken in the evening or late afternoon will differ, the latter being usually higher.

The variations in the supplemental pressure (casual minus basal) represent the response of the patient to his own activities and to his environment. Many of the variations are reactions of the mind and concerned with emotional responses and reactions of alertness.

### Effect of Mental Work

Hill (1898), Bickel (1914), and Gillespie (1924) have reported that mental work elevates the blood pressure. Fischer (1930) says that

mental exertion unaccompanied by emotion — he refers to games of chess — have no effect on the blood pressure.

My impression is that the variable results reported concerning the effect of mental work on the blood pressure level may depend essentially on different ways in which mental work is performed. Some people engaged in mental activity are tense muscularly, alerted and unrelaxed, even if emotion as ordinarily understood is lacking. Such habits might be modified during a deliberate experiment. In any case unemotional mental work has no large effect on blood pressure levels.

### Effect of Sleep

Perhaps the first observations on the effect of sleep on the blood pressure were those reported by Tarchanoff (1894) to an International Congress of Medicine in Rome. While recording the carotid artery pressure kymographically, he had been able to persuade young pups to go to sleep by petting, and had noted a blood pressure fall of between 20 and 50 mm In man Howell (1897) demonstrated dilatation of limb vessels during sleep. Falls of blood pressure during sleep were demonstrated by Hill (1898), Brush and Fayerweather (1901), Brooks and Carroll (1912), Muller (1921), Katsch and Pansdorf (1922), Landis (1925), Allbutt (1925) and Blankenhorn and Campbell (1925). Brooks and Carroll (1925) observed on an occasion when a ward had been disturbed by a delirious patient that other patients, who had slept despite the disturbance, showed a smaller drop during sleep than they had exhibited before. MacWilliam (1923) cited occasions in which the blood pressure during sleep was taken when a nightmare was in progress. Blood pressures as high as 200 mm. systolic were recorded. It is of interest that Brooks and Carroll (1912) and Müller (1921) noted much bigger blood pressure falls during sleep when the blood pressure was high than when it was average.

It will be seen in Table IV 1 that, when the blood pressure starts at a high level, the falls of blood pressure during undisturbed sleep are greater than when the initial blood pressure is low.

It appears to be agreed by almost all observers that, in young normotensives, the systolic blood pressure during sleep falls usually to between 90 and 105 mm. Hg and the diastolic blood pressure is often between 60 and 75 mm. Hg These pressures are evidently below ordinary casual blood pressure levels but they are in the usual range of basal blood pressures for persons whose casual blood pressures are in a fully normal range Alam and Smirk (1943) noted that when basal blood pressures were being taken, with blood pressure measurements made regularly at about 20-second intervals, the patient would sometimes fall asleep for a few minutes without there being any further fall in the blood pressure level, and this has been reconfirmed in the course of work referred to in the previous chapter. We had no

TABLE IV 1. *Blood Pressure During Sleep*

| Average B P. Awake | Average B.P. Asleep | Average B P. Fall | Remarks | Authors |
|---|---|---|---|---|
| 112/— | 101/— | 11/— | corrected for posture, average of 25 subjects, normal sleep | Blankenhorn and Campbell, 1925 |
| 110/54 | 94/58 | 16/4 | male students | Landis, 1925 |
| | | | with nightmares and disturbed sleep B.P. up to 200 systolic | MacWilliam, 1923 |
| 100/— | 83.5/— | 16.5/— | 30 patients with low B.P. | Brooks and Carroll, 1912 |
| 142.5/— | 118.5/— | 24/— | 68 patients with medium B.P. | Brooks and Carroll, 1912 |
| 204 5/— | 159.7/— | 44.8/— | 29 patients with high B.P. | Brooks and Carroll, 1912 |
| — | — | 9.8/— | | Brush and Fayerweather, 1901 |
| 185/— | 137/— | 48/— | 10 hypertensives | Müller, 1921 |
| 154/— | 126/— | 28/— | 11 patients with intermediate pressures | Müller, 1921 |

observations which would enable us to comment on the possibility of further falls of blood pressure with sleep of longer duration.

## Effect of Exercise

Thacker (1940) studied the effect of exercise in university students. His series included 96 with overaverage pressures, 128 normal and 56 hypotensive subjects. The average systolic blood pressure increases with exercise were 48, 37 and 23 mm. respectively for the three groups. Norris, Shock and Yiengst (1953) studied the effect of mild exercise in male subjects The systolic blood pressure in the older patients started at a higher level and rose more after the exercise than in the younger subjects. There was little difference in the effects of exercise on the diastolic blood pressures. The return of the blood pressure towards the original level was slower in the older subjects than in the younger subjects Hood et al. (1953) observed the effect upon hypertensives of an exercise on a bicycle ergometer equivalent to very moderate uphill cycling. From starting levels in the region of 200 systolic the systolic blood pressure rises averaged 50 or 60 mm. The diastolic blood pressures rose by 10 or 15 mm. Following the exercise there was usually a drop below the original level. These observations [illegible]

It is generally agreed that the systolic blood pressure and the pulse pressure increase during exercise, but there is difference of opinion concerning the diastolic pressure. Christensen (1945) reported an increase of the diastolic pressure with five minutes or more of steady bicycle-type exercise. Simonson and Enzer (1942) thought that the diastolic pressure either remained constant or increased slightly during exercise. It has been reported by others that it shows no change (Glaser, 1951; and Nielsen, 1937). Fraser and Chapman (1954) reported falls in the diastolic pressure during walking exercise.

Fraser and Chapman (1954) used intra-arterial recordings of the blood pressure while the subject walked for [illegible]

[illegible] described the changes in blood pressure in a bicycle sprint exercise The systolic blood pressure rose, the diastolic blood [illegible] recorded during the [illegible] immediate post-exer[illegible] and after the exercis[illegible] immediately after th[illegible]

rapidly, but not all the way towards normal, and then rose again graduall regaining a normal level after six or seven minutes. With longer term exerci the post-exercise trough of blood pressure is not as prominent as after sprin exercise.

Wheeler et al. (1956) found that exercise decreased the estimated hepat blood flow (Bromsulfalein) by 240—460 ml./min. The splanchnic blood volun (by regional dilution of $I^{131}$ albumin) showed a decrease of 285—700 ml. The changes would have the effect of increasing the return of venous blood to th heart and making more blood available to the voluntary muscles

The suggestion was made by Alam and Smirk (1937) that a signifi cant part of the blood pressure rise which occurs during exercise ma *result from a blood pressure raising reflex arising from voluntar* muscles and associated with the accumulation within the muscles o exercise metabolites. When the exercise is severe ischaemic pai occurs. It was shown that exercise short of pain also gave rise to refle blood pressure increases. Subsequently it was shown [2] that the respons *to the blood pressure raising reflex from muscle was larger in olde* than in young people, as was also the response to the cold presso reflex. The rises of blood pressure in essential hypertension were a an average greater than those in normotensive subjects in the sam age group, and much greater than in patients with renal hypertension *These comparisons, however, were between groups, and individua* experiments were encountered with large rises of blood pressure in normal subjects and with small rises of blood pressure in patients wit essential hypertension. Korner (1952), in experiments with bicycl exercise, showed that arrest of the circulation through muscles, a *various times after the cessation of exercise, prevented the furthe* fall of the blood pressure towards normal during the post-exercis recovery period. He attributed this to the above mentioned reflex which was stimulated by failure to disperse the metabolites.

The *general impression is that the systolic* pressure is raised by exercise, and to a much greater extent in hypertensives than in normotensives. The diastolic pressure may rise or fall according to the circumstances. The pulse pressure is increased. Increase in cardiac output is an important cause for the blood pressure increase but reflexes dependent on the accumulation of muscle metabolites play a part.

## Effect of Muscular Tension and Relaxation

*Jacobson (1939) investigated the relationship between the* blood pressure level and voluntary muscle tension as judged by muscle action potentials. Muscle action potentials show that so-called "rest" in the horizontal posture is not necessarily associated with relaxation of muscle tension. When, however, a degree of relaxation is obtained, *in which* the recorded action potentials are diminished, then falls of blood pressure are noted. Jacobson considers that at any given

moment the level of the blood pressure in essential hypertension is influenced to an important degree by the state of muscle tension. He thinks that it is possible that persistent increase in muscle tension may favour the development of essential hypertension.

## Effect of Posture

In healthy individuals and in most untreated hypertensives, the effects upon the circulation of changes in posture are neutralized by alterations in the activity of the sympathetic nervous system, so that large blood pressure changes are not observed in the arm held at heart level. In health, the sudden assumption of the erect posture usually leads to a fall in the blood pressure for a few seconds, followed by a prompt return to a normal level, or, momentarily, to a higher level. If a person is placed on a tilting table and tilted rapidly from the horizontal to the vertical posture the blood pressure falls, then for about a minute rises above the baseline level and falls again (Wilkins et al., 1948). The overshoot above the baseline pressure depends upon the activity of the [illegible]

[illegible] when a person stands the blood pressure has attained approximately the same level as in the lying posture within a minute or so. The range of variation up or down is somewhat greater in hypertensives than in normotensives, and hypertensives may exhibit systolic rises of as much as 20 or falls of as much as 20 mm. Hg and sometimes more. The diastolic pressure changes are smaller. Long standing without muscular movements gives rise to syncope and a fall of blood pressure.

In the standing posture the cardiac output falls (McMichael and Sharpey-Schafer, 1944; Stead et al., 1945), consequently the pulse pressure is usually reduced. As sympathetic vasoconstriction compensates for decreased cardiac output (Brigden et al., 1950) it is usually found that the diastolic pressure rises a little in the erect posture

Norris, Shock and Yiengst (1953) studied the effect of change of posture upon the blood pressure in three groups of subjects aged 20 to 29, 60 to 69, and 80 to 92 years They noted that a position change from the horizontal to a 45 degree tilt caused a decrease of the systolic pressure and no change in the diastolic pressure With this degree of tilt the older subjects showed a greater drop in the systolic levels than did the young subjects. The diastolic levels remained unchanged The heart rate increased more in the young subjects

Following a tilt into the standing position the [illegible]

Postural hypotension may occur on standing after a prolonged hot bath, for example, 20 minutes at 40 degrees Centigrade (Horvath, 1948), and also after breathing a gaseous mixture deficient in oxygen, such as 8 per cent oxygen, 92 per cent nitrogen (Gellhorn, 1937). Kalser et al. (1954) refer to the development of postural hypotension in man following 2 mg. of atropine sulphate.

Other postures inducing circulatory effects which might lower the blood pressure are lordosis, and the strict supine posture in pregnancy. These postures decrease the cardiac output (Brigden et al., 1950), presumably by pressure exerted on the inferior vena cava.

*Idiopathic postural hypotension.* — Laubry in 1924 described a case of idiopathic hypotension. Bradbury and Eggleston (1925) appear to have been the first to describe the occurrence of anhidrosis and impotence in association with spontaneous postural hypotension, and a more complete description has been published by East and Brigden (1946). Rosecan et al. (1952) noted a similar association in their cases. They made the interesting observation that while overheating did not induce sweating, pilocarpine did. The sweat glands and nerve endings appear, therefore, to have maintained their activity. The presumption that spontaneous postural hypotension is due to inactivity of the sympathetic nerves has been confirmed by Luft and von Euler (1953) who found a marked decrease in the urinary catecholamines. The increase in catecholamines which normally follows an injection of histamine, was also lacking. Benestad and Bøe (1954) also found a decrease in the urinary catecholamines in a case of idiopathic postural hypotension. Barnett et al. (1955) described four patients and showed that there is a variation from case to case in the extent to which the various sympathetic functions are impaired

Verel (1951) described three cases of postural hypotension. In each case vasoconstriction following a deep breath could be demonstrated. This demonstrates the preservation of certain sympathetic reflexes at a time when others are lost.

Hickam and Pryor (1951) studied the cardiac output in patients suffering from postural hypotension They had 12 patients — 3 were idiopathic, 5 were associated with diabetes mellitus, 2 with tabes dorsalis, 1 with probable syringomyelia and 1 followed bilateral sympathectomy The authors concluded that there could be well-marked postural hypotension with no more than the normal postural decrease in cardiac output. They thought that the postural hypotension in these cases was due to failure of arteriolar constriction There were, however, some patients who exhibited overaverage decreases in the [illegible] large infusions of serum [illegible] well maintained [illegible] deficiency in the venous tone. Stead and Ebert (1941), however, [illegible] that in patients with postural hypotension the amount of blood pooled in the lower limbs during

standing did not exceed the normal. The blood pressure fall was due to inability to compensate by sympathetic vasoconstriction for the normal amount of blood which pooled in the legs.

Further reference is made later to postural hypotension induced by methonium salts (Chapter XVIII), sympathectomy (Chapter XIV), salt deprivation (Chapter XV), and blood loss (Chapter IV).

## Effect of Breath-Holding

Ayman and Goldshine (1939) observed the effect of breath-holding with nostrils and mouth compressed but without inhaling or exhaling. Patients were asked not to take a preliminary breath but to hold the breath for twenty seconds. The systolic blood pressure was noted at the end of twenty seconds. The test was then repeated and the diastolic blood pressure determined. The test was performed on 55 persons with normal blood pressure and 95 with essential hypertension. The [illegible]

[illegible] who were hyporeactors to the test with mean blood pressure rises of 11.6/11.7 mm. Hg and 9 normotensives were hyperreactors with mean pressure rises of 32.0/21.0 mm. Hg. Ninety-five hypertensives who had fallen to a steady level before the test had a mean rise in blood pressure of 40 7/25.4 mm. Hg.

Feldt and Wenstrand (1941) used a technique very similar to that of Ayman and Goldshine. They found that the responses of the blood pressure to the cold pressor and the breath-holding test were closely related. There were, however, wide differences between the two tests in individual persons and an increased reaction to one of the tests might be associated with a decreased reaction to the other. The mean blood pressure increases obtained by these authors were: in normal hyporeactors 13 23/12.19 mm. Hg, in normal hyperreactors 26.85/21.71 mm Hg, in hypertensives 28.47/21 47 mm. Hg.

## Effect of Hyperventilation

During one minute of overbreathing Burnum et al. (1954) found that the mean arterial pressure fell in [illegible] maximal fall was 18 mm. Hg in [illegible] ventilation is due to the washing [illegible] carbon dioxide causes a rise of [illegible] pressure which is greater in essential hypertension than in health. In idiopathic hypotension, hyperventilation precipitates orthostatic collapse (Laplace, 1942; Burnam, Hickam and Stead, 1954).

Postural hypotension may occur on standing after a prolonged hot bath, for example, 20 minutes at 40 degrees Centigrade (Horvath, 1948), and also after breathing a gaseous mixture deficient in oxygen, such as 8 per cent oxygen, 92 per cent nitrogen (Gellhorn, 1937). Kalser et al. (1954) refer to the development of postural hypotension in man following 2 mg. of atropine sulphate.

Other postures inducing circulatory effects which might lower the blood pressure are lordosis, and the strict supine posture in pregnancy. These postures decrease the cardiac output (Brigden et al., 1950), presumably by pressure exerted on the inferior vena cava.

*Idiopathic postural hypotension.* — Laubry in 1924 described a case of idiopathic hypotension. Bradbury and Eggleston (1925) appear to have been the first to describe the occurrence of anhidrosis and impotence in association with spontaneous postural hypotension, and a more complete description has been published by East and Brigden (1946). Rosecan et al. (1952) noted a similar association in their cases. They made the interesting observation that while overheating did not induce sweating, pilocarpine did. The sweat glands and nerve endings appear, therefore, to have maintained their activity. The presumption that spontaneous postural hypotension is due to inactivity of the sympathetic nerves has been confirmed by Luft and von Euler (1953) who found a marked decrease in the urinary catecholamines. The increase in catecholamines which normally follows an injection of histamine, was also lacking. Benestad and Bøe (1954) also found a decrease in the urinary catecholamines in a case of idiopathic postural hypotension. Barnett et al. (1956) described four patients and showed that there is a variation from case to case in the extent to which the various sympathetic functions are impaired.

Verel (1951) described three cases of postural hypotension. In each case vasoconstriction following a deep breath could be demonstrated. This demonstrates the preservation of certain sympathetic reflexes at a time when others are lost.

Hickam and Pryor (1951) studied the cardiac output in patients suffering from postural hypotension They had 12 patients — 3 were idiopathic, 5 were associated with diabetes mellitus, 2 with tabes dorsalis, 1 with probable syringomyelia and 1 followed bilateral sympathectomy The authors concluded that there could be well-marked postural hypotension with no more than the normal postural decrease in cardiac output They thought that the postural hypotension in these cases was due to failure of arteriolar constriction There were, however, some patients who exhibited overaverage decreases in the [illegible] of serum [illegible]

venous tone Stead and Ebert (1941), however, considered that in p[illegible] with postural hypotension the amount of blood pooled in the lower limbs during

standing did not exceed the normal. The blood pressure fall was due to inability to compensate by sympathetic vasoconstriction for the normal amount of blood which pooled in the legs.

Further reference is made later to postural hypotension induced by methonium salts (Chapter XVIII), sympathectomy (Chapter XIV), salt deprivation (Chapter XV), and blood loss (Chapter IV).

### Effect of Breath-Holding

Ayman and Goldshine (1939) observed the effect of breath-holding with nostrils and mouth compressed but without inhaling or exhaling. Patients were asked not to take a preliminary breath but to hold the breath for twenty seconds. The systolic blood pressure was noted at the end of twenty seconds. The test was then repeated and the diastolic blood pressure determined. The test was performed on 55 persons with normal blood pressure and 95 with essential hypertension. The responses indicate a similarity between the cold pressor test and the breath-holding test. Thirty-seven out of 44 patients had excessive reactions to both tests. The rise of pressure was much greater in hypertension and sometimes the pressure rose to great heights. There were 46 normotensives who were hyporeactors to the test with mean blood pressure rises of 11.6/11.7 mm Hg and 9 normotensives were hyperreactors with mean pressure rises of 32.0/21.0 mm. Hg. Ninety-five hypertensives who had fallen to a steady level before the test had a mean rise in blood pressure of 40.7/25 4 mm. Hg.

Feldt and Wenstrand (1941) used a technique very similar to that of Ayman and Goldshine. They found that the responses of the blood pressure to the cold pressor and the breath-holding test were closely related There were, however, wide differences between the two tests in individual persons and an increased reaction to one of the tests might be associated with a decreased reaction to the other. The mean blood pressure increases obtained by these authors were: in normal hyporeactors 13 23/12 19 mm. Hg, in normal hyperreactors 26.85/21.71 mm Hg, in hypertensives 28.47/21 47 mm Hg.

### Effect of Hyperventilation

During one minute of overbreathing Burnum et al. (1954) found that the mean arterial pressure fell in 33 out of 35 subjects. The [illegible] maximal fall was 18 mm Hg i[illegible] ventilation is due to the washi[illegible] carbon dioxide causes a rise [illegible] which is greater in essential hypertension than in health. In idiopathic hypotension, hyperventilation precipitates orthostatic collapse (Laplace, 1942; Burnam, Hickam and Stead, 1954).

## *Effect of Expiration with Closed Glottis (The Valsalva Manoeuvre)*

During expiration with closed glottis the intrathoracic pressure, normally negative, may become positive, the return of blood to the right auricle is delayed and the venous pressure rises and may exceed 30 cm. of water. The blood pressure and the pulse pressure both decrease, largely due to diminished cardiac output. In hypertension the blood pressure fall may be very great, even as much as 60 or 80 mm Hg in the systolic and perhaps half this in the diastolic pressure. Following cessation of the expiratory effort the blood pressure rises well above the original level, particularly the systolic, which may be elevated 50 or 70 mm. Hg. Following extensive surgical sympathectomies or the use of ganglion blocking agents, the blood pressure fall still takes place, but the reactionary rise of blood pressure after cessation of the expiratory effort no longer occurs or is much reduced (Wilkins et al., 1948).

Hamilton et al (1936) describe four phases of the Valsalva manoeuvre, (1) blood pressure increases, (2) blood pressure falls, (3) blood pressure falls precipitously, (4) blood pressure rises again. Rushmer (1947) distinguishes between the effect of Vi and Ve manoeuvres in which the effort was made with the lungs in inspiration and in expiration respectively. The effect of the Vi manoeuvre was as follows — a slight rise of pressure of short duration followed by a more marked fall, particularly in the systolic blood pressure. After the manoeuvre ended the systolic and diastolic pressures rose above the original level with an increase of pulse pressure. During the Ve manoeuvre the fall of blood pressure was not as great as during the Vi manoeuvre

In a subject with a history of dizziness on standing erect Rushmer (1947) found that the manoeuvre caused a response similar to that in circulatory collapse Corresponding findings are those of MacLean et al. (1944) who used the Valsalva manoeuvre to demonstrate orthostatic hypotension Positive pressure breathing by mechanical respirators may also cause an important fall in the blood pressure, especially in anaesthetized patients (Price et al, 1952)

Sarnoff et al. (1948) studied the Valsalva test in dogs The response of the arterial pressure had six components The overshoot was thought to be the result of reflex sympathetic activity Impairment of carotid sinus activity diminished the overshoot as did also the presence of an excess of circulating epinephrine

## Effect of Coughing

The act of coughing, involving as it does wide swinging variations in the intrathoracic pressure, may cause both rises and falls in the blood pressure. A study of the mechanism of coughing has been reported by Sharpey-Schafer (1953). Not infrequently, shortly after coughing starts, there is a rise of pressure but this is followed by a fall in the blood pressure below normal, which occasionally causes faintness or syncope. Sharpey-Schafer (1953) found that a single

cough may raise the intrathoracic pressure by 20 to 30 mm. Hg, ordinary coughing may cause a rise of 60 to 100 mm. Hg and violent coughing, which is more likely to lead to a syncopal attack, may be associated with a rise of 150 to 300 mm. Hg. in the intrathoracic pressure. The effects of coughing are not unlike those of the Valsalva manoeuvre but in this latter the intrathoracic pressure seldom rises above 100 mm. Hg. The fall of blood pressure seems to be greater than is ordinarily encountered during the Valsalva manoeuvre, a probable reason being that the intermittent changes of pressure induced by the coughing stimulate baroceptors of the carotid sinus leading to peripheral vasodilatation. A fall of blood pressure after vigorous coughing is usual. Syncope is not very uncommon.

### Effect of Inspiration with Closed Glottis (The Müller Manoeuvre)

Very little has been written about the Müller manoeuvre. Experiments in our laboratory (Irvine, Unpublished) suggest that in normals there is a prompt fall of blood pressure which rises again at the end of the inspiratory phase and sometimes overshoots the original level. The overshoot is not very different from that observed during simple breath-holding. Similar results were obtained by Mechelke and Nusser (1953) The fall of blood pressure is probably due to blood being trapped in the great veins, the lungs and the right side of the heart.

### Effect of Defaecation

It would seem probable that physiologically, so far as concerns respiration and the circulation, defaecation is very similar to the Valsalva manoeuvre. In normal subjects we found the blood pressure changes during defaecation were of the same order as those encountered with corresponding effort applied to the Valsalva manoeuvre. The overshoot at the end of the expiratory effort may produce a dangerous rise of pressure in hypertensives. Even in normotensives the systolic blood pressure may rise above 180 mm. Hg.

### Effect of Parturition

Vaquez in 1900 described considerable blood pressure increases during parturition The expulsive effort during emergence of the head was found to be associated with systolic blood pressures of as much as 180 or even 250 mm Hg.

### Effect of Meals

The consumption of food promotes vasodilatation and increase in the flow of blood through the digestive tract. It is not surprising, therefore, that the cardiac output and the pulse pressure increase (Grollman, 1929). The systolic pressure commonly rises a little and the

diastolic pressure may be unchanged or fall. In some instances the blood pressure falls; doubtless this occurs when alimentary vasodilatation is the principal response to food intake. May (1929) had also noted the increase in pulse pressure. The consumption of large volumes of fluid may elevate the blood pressure. The effects of variations in the salt intake are referred to in Chapter XV.

In patients under methonium compounds, compensatory reflexes are blocked and a fall of blood pressure after a meal is an almost constant finding. Sometimes the fall is large, even causing faintness.

### Effect of Starvation and of the Subsequent Restoration of Food

Great interest attaches to changes of living conditions which alter the level of the blood pressure and the incidence of hypertension of substantial population groups. During the 1945 famine in Western Holland, Burger et al. (1945) often found systolic pressures down to 80 mm. Hg and heart rates down to 40 per minute.

During this famine Lups and Francke (1946) examined 520 persons attending the poly-clinic before and at the height of the famine and recorded the averages of the blood pressures encountered. There would appear to be a decrease at all ages.

TABLE IV 2. *Mean Blood Pressures, in mm. Hg, in 520 persons seen at the poly-clinic in Utrecht before and at the height of the famine period (Lups and Francke, 1946)*

| Age (yrs) | Before September 1944 | | April 1945 | |
|---|---|---|---|---|
| | Systolic | Diastolic | Systolic | Diastolic |
| 20—30 | 132±12 | 77±10 | 125±13 | 70± 9 |
| 30—40 | 132±14 | 79±10 | 121±12 | 71± 9 |
| 40—50 | 133±17 | 80±12 | 126±18 | 72±15 |
| 50—60 | 146±26 | 85±15 | 129±28 | 77±14 |
| 60—75 | 164±32 | 88±16 | 144±31 | 76±14 |

Schrader (1952) referred to the effect of restoration of food upon the blood pressure level in peoples who had undergone a period of severe undernourishment. During the period of starvation the blood pressure was reduced below normal During the stage of healing, the previously depressed blood pressure often rose above the normal and in some instances to hypertensive levels. He noted that sometimes the elevated blood pressure had not returned to normal in 1 to 2 years. Sixteen of a series of 200 patients developed hypertension and half of these were men of 40 to 50 years, the average pressure being 176/112. Slight increases of pressure after return to a full diet were reported in the British Medical Research Council Monograph. Evidently there

is not always a dramatic increase in the incidence of hypertension after restoration of food to a deprived population. Falls of blood pressure under conditions of famine or defective nutrition have also been reported by Spies and Stone (1949), Per Helweg-Larsen et al. (1952), Zimmer et al. (1944), Leyton (1946) and Howarth, in a British Medical Research Council Monograph (1951).

Experiments by Keys et al. (1950) on human volunteers indicate that deprivation of food reduces blood pressure levels when other living conditions are good The diet was designed to represent the types of food available in famine areas of Europe and it contained 1570 calories, including 50 gm. of protein and 30 gm. of fat. The initial mean blood pressure in the control period was in the low normal range, namely 106 5/69.7 mm. Hg and at the 23rd week of deprivation the mean pressure had fallen to 94.7/64.4 mm. Hg, the number of definite hypotensives had increased and the pulse rate had diminished appreciably. The difference between control and starvation blood pressures was probably lessened by the choice of subjects with low normal levels initially.

There are few reports on complete deprivation of food but blood pressure changes in a "hunger artist" (hungerkünstler) were recorded by Kanzow (1951) who noted a fall from a level of 135/90 on the thirteenth hunger day to 110/70 on the forty-eighth day.

We are indebted to Brozek et al. (1948) for publishing an account of the reports by Leningrad physicians during the war years. During severe dietary limitation there was a decrease of blood pressure and a decreased incidence of hypertension. When food became more plentiful the general level of the blood pressure increased and the incidence of hypertension increased greatly with a substantial rise of the death rate. At the Erisman Hospital in Leningrad 1.2 to 5.2 per cent of all autopsies were carried out on hypertensives, but after food supplies increased 54.5 per cent of total autopsies were on hypertensive persons Exudative retinal changes, including papilloedema, were present before the war in 23 to 25 per cent of patients admitted for hypertensive disease. This figure rose to 70 per cent during the post-starvation period.

In Japan, Itahara et al. (1955) found a decrease in the incidence of hypertension during the war years, when food was deficient. The incidence of hypertension rose again when food became more freely available, but no mention is made of a rise above the pre-war level

## Effect of Blood Loss

Venesections with removal of 400 ml. of blood may reduce the blood pressure for a few days in hypertensive patients, even in malignant hypertension. Loss of over 1000 ml. may cause a pronounced

diastolic pressure may be unchanged or fall. In some instances the blood pressure falls; doubtless this occurs when alimentary vasodilatation is the principal response to food intake. May (1929) had also noted the increase in pulse pressure. The consumption of large volumes of fluid may elevate the blood pressure. The effects of variations in the salt intake are referred to in Chapter XV.

In patients under methonium compounds, compensatory reflexes are blocked and a fall of blood pressure after a meal is an almost constant finding. Sometimes the fall is large, even causing faintness.

### Effect of Starvation and of the Subsequent Restoration of Food

Great interest attaches to changes of living conditions which alter the level of the blood pressure and the incidence of hypertension of substantial population groups. During the 1945 famine in Western Holland, Burger et al. (1945) often found systolic pressures down to 80 mm. Hg and heart rates down to 40 per minute.

During this famine Lups and Francke (1946) examined 520 persons attending the poly-clinic before and at the height of the famine and recorded the averages of the blood pressures encountered. There would appear to be a decrease at all ages.

TABLE IV 2. *Mean Blood Pressures, in mm. Hg, in 520 persons seen at the poly-clinic in Utrecht before and at the height of the famine period (Lups and Francke,* 1946)

| Age (yrs) | Before September 1944 | | April 1945 | |
|---|---|---|---|---|
| | Systolic | Diastolic | Systolic | Diastolic |
| 20—30 | 132±12 | 77±10 | 125±13 | 70± 9 |
| 30—40 | 132±14 | 79±10 | 121±12 | 71± 9 |
| 40—50 | 133±17 | 80±12 | 126±18 | 72±15 |
| 50—60 | 146±26 | 85±15 | 129±28 | 77±14 |
| 60—75 | 164±32 | 88±16 | 144±31 | 76±14 |

Schrader (1952) referred to the effect of restoration of food upon the blood pressure level in peoples who had undergone a period of severe undernourishment. During the period of starvation the blood pressure was reduced below normal. During the stage of healing, the previously depressed blood pressure often rose above the normal and in some instances to hypertensive levels. He noted that sometimes the elevated blood pressure had not returned to normal in 1 to 2 years. Sixteen of a series of 200 patients developed hypertension and half of these were men of 40 to 50 years, the average pressure being 176/112. Slight increases of pressure after return to a full diet were reported in the British Medical Research Council Monograph. Evidently there

## Effect of Tea, Coffee and Alcohol

In normal amounts the effects of tea and coffee are unimportant. In excessive amounts they may contribute to nervousness or sleeplessness. According to Horst and co-workers (1934, 1935) consumption of coffee in large amounts may raise the systolic blood pressure by 5 or 10 mm. Hg. It is generally agreed that alcohol consumption has no important immediate or delayed effect upon the blood pressure level under ordinary circumstances. In so far as alcohol induces peripheral dilatation and sedation it may tend to slight lowerings of the blood pressure; in so far as it may contribute towards obesity it may lead to increases of the blood pressure. Fishberg (1954) states that alcoholic derelicts in New York City have a tendency to low rather than to high blood pressures. It has been known for some time that the blood pressure tends to be a little lower than the average in patients with hepatic cirrhosis, and recently it has been noted that liver damage resulting from infective hepatitis is commonly associated also with slightly lower levels of the blood pressure.

## Effect of Nicotine and Tobacco

Nicotine stimulates the vasoconstrictor and emetic centres in the medulla and the sympathetic and parasympathetic ganglia. Stimulation is followed by a pronounced depression of ganglionic activity. Nicotine can also cause increased release of adrenaline and probably of noradrenaline from the suprarenal glands. It will be recognized that no simple response can be expected from a drug with such complex actions. In experimental animals the injection of small doses of nicotine tartrate is likely to elevate the blood pressure but large doses cause a decrease.

Small doses of nicotine have been administered in man by Maddock and Coller (1953) who state that intravenous doses of 1.5 to 6 mg. give rise to small blood pressure increases. It seems likely that the effect of tobacco smoke is due mainly to its nicotine content. Most observations concern the smoking of tobacco. In novices Dixon (1927) found rises of systolic pressure of 20 to 25 mm. but there was little action in habitual smokers Other authors [37, 44, 73] have described small blood pressure increases in habitual smokers

Oliver (1916) stated that normal subjects not habituated to smoking almost always had a rise in the systolic pressure after smoking of 10 to 20 mm Hg without a correspond[illegible] He notes, however, that with regular [illegible] there may be a low blood pressure. Hir[illegible] blood pressure rises in hypertensives [illegible] in normotensives. In 26 normotensive patients with labile blood pressures Roth (1954) found that the systolic pressure might increase by an average of 38 mm. Hg

fall of blood pressure, even in the horizontal posture (Wallace and Sharpey-Schafer, 1941). Assumption of the sitting posture is then followed by additional falls of blood pressure and fainting. The fainting is associated with an increase of blood flow in a normally innervated forearm, but not in a sympathectomized forearm (Barcroft and Edholm, 1946; Barcroft and Swan, 1953) (Fig. IV 1). Evidently, when

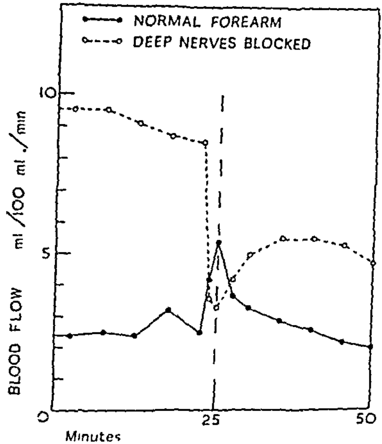



Fig IV 1

[illegible] ic [illegible] blc [illegible] explained by active vasodilatation in the normal forearm excited by sympathetic vasodilator fibres (Barcroft, H., and Swan, H. J C, Sympathetic Control of Human Blood Vessels, Edward Arnold & Co, London, 1953)

fainting occurs, there is loss of the compensatory sympathetic vasomotor tone which has limited the extent of the blood pressure fall. Probably also there is vasodilatation from increased activity of vasodilator nerves.

Taylor and Noble (1950) describe the appearance of an antidiuretic substance in the urine on fainting. My colleagues Dr. Field and Mr. Laverty find that when anaesthetized rats are bled there is a considerable release of pressor substances into the blood stream.

11 BENESTAD, A M., and BØE, J. Idiopathic orthostatic hypotension — Clinical and laboratory studies with report of a case. Acta med. scand., 150, 1, 1954.

12 BICKEL, H Über die normale und pathologische Reaktion des Blutkreislaufs auf psychische Vorgänge. Neurol Zbl, 33: 90, 1914.

13 BLANKENHORN, M. A, and CAMPBELL, H. E The effect of sleep on blood pressure Amer. J. Physiol, 74: 115, 1925

14 BRADBURY, S, and EGGLESON, C. Postural hypotension — A report of three cases Amer. Heart J, 1: 73, 1925

15 [illegible] ... 9, 79, 1950

16 BROOKS, H, and CARROLL, J H. A clinical study of the effects of sleep and rest on blood pressure Arch intern Med, 10: 97, 1912.

17 BROZEK, J, CHAPMAN, C. B and KEYS, A Drastic food restriction: Effect on cardiovascular dynamics in normotensive and hypertensive conditions J. Amer. med Ass, 137 1569, 1948.

18 BRUSH, C E, JR, and FAYERWEATHER, R Observation on the changes in blood-pressure during normal sleep Amer. J. Physiol, 5, 199, 1901.

19 BURGER, G C. E., SANDSTEAD, H. R., and DRUMMOND, J. Starvation in western Holland Lancet, 2: 282, 1945.

20 BURNUM, J F, HICKAM, J B, and MCINTOSH, H. D. The effect of hypocapnia on arterial blood pressure Circulation (N.Y.), 9: 89, 1954.

21 BURNUM, J F, HICKAM, J B, and STEAD, E A. JR. Hyperventilation in postural hypotension Circulation (N Y), 10: 362, 1954.

22 CHRISTENSEN, B C Studies on the effort syndrome. I. The patients' capacity for work and the variations in the arterial pressures and pulse rate during muscular work compared with conditions found in normals. Acta med scand, 121 194, 1945

23 DIXON, W. E The physiological effects of smoking. Practitioner, 118: 20, 1927

24 EAST, T., and BRIGDEN, W Postural hypotension. Brit. Heart J., 8: 103, 1946

25 FELDT, R H, and WENSTRAND, D E. W The cold pressor and breath-holding test Arch intern Med, 67 1157, 1941.

26 FISCHER, R Über das Verhalten des Blutdruckes bei geistiger Anstrengung. Med Klin, 26. 625, 1930

27 FISHBERG, A. M Hypertension and nephritis Lea and Febiger, Philadelphia, 1954, 5th edn.

28 FRASER, R S, and Chapman, C B. Studies on the effect of exercise on cardiovascular function II The blood pressure and pulse rate Circulation (N Y), 9 193, 1954.

29 GELLHORN, E Circulatory studies on anoxemia in man with respect to posture and carbon dioxide. Ann intern Med., 10: 1267, 1937.

30 GILLESPIE, R D The relative influence of mental and muscular work on the pulse-rate and blood-pressure J. Physiol (Lond.), 58 425, 1924.

31 GLASER, E M Response of the blood pressure and pulse rate to postural changes and exercise. Special Report No 275, Medical Research Council, 1951, p. 280 His Majesty's Stationery Office, London.

32 GROLLMAN A [illegible] III [illegible] man. rate, [illegible] pulse Phys [illegible] Amer. J.

33 HAMILTON, W F, WOODBURY, R A, and HARPER, H. T., JR Physiologic

(range 24 to 57 mm.) and the diastolic pressure by an average of 30 mm. Hg (range 18 to 35 mm.).

In patients with hypertension Roth (1954) found the average increase of pressure with smoking one standard cigarette was 38 mm. systolic, 23 mm. diastolic. For this reason Roth thinks it desirable to advise hypertensive patients to stop smoking. It should be noted that Roth allows her patients to approach basal levels before smoking — hence she records rather large rises. In an early report Thompson and Sheldon (1917) say that in patients with high blood pressure the maximum response to smoking ranged from a rise of 35 mm. to a fall of 30 mm. in the systolic pressure.

The effect of smoking on the blood pressure appears to vary. When the rises of pressure are small they can be overcome by the use of hypotensive agents and it is not usually necessary to forbid smoking in hypertensive patients for any effect it may have on blood pressure. The statistics of life insurance companies, however, show that the incidence of cardiovascular complaints is higher in smokers than in non-smokers, and life expectancy is less in heavy smokers. Reduction or elimination of tobacco consumption may be justified in some patients on grounds of general health. It must be remembered that to abstain from smoking may be hard for a patient who is already leading a restricted life.

## References

1 Alam, G M, and Smirk, F H Observations in man upon a blood pressure raising reflex arising from the voluntary muscles J Physiol (Lond.), 89: 372, 1937

2 Alam, G. M., and Smirk, F. H Blood pressure raising reflexes in health, essential hypertension, and renal hypertension Clin Sci, 3 259, 1938.

3 Alam, G M, and Smirk, F. H. Casual and basal blood pressures II In essential hypertension Brit Heart J, 5 156, 1943.

4 Allbutt, T. Arteriosclerosis Macmillan & Co, London, 1925.

5 Ayman, D Heredity in arteriolar (essential) hypertension. A clinical study of the blood pressure of 1,524 members of 277 families Arch intern Med., 53· 792, 1934

6 Ayman, D, and Goldshine, A D. The breath holding test. Arch intern. Med., 63· 899, 1939

7 Barath, E Arterial hypertension and physical work Arch intern Med., 42: 297, 1928

8 Barcroft, H, and Edholm, O G On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting J Physiol. (Lond ), 104 161, 1945

8a Barcroft, H, and Swan, H J C Sympathetic control of human blood vessels Edward Arnold & Co, London, 1953

9 Barnett, A J, Hamilton, M D, and Kay, H B Severe orthostatic hypotension. Aust Ann Med, 4· 183, 1955

10 Bauer, J, and Neuburger, F Die Blutdruckreaktion auf korperliche Arbeit bei abnormen Blutdruck Z klin Med, 120: 628, 1932.

G. Doin, édit., Paris, 1924. Cited by Laubry, C., and Doumer, E., Press méd., 40: 17, 1932.

55 LAUBRY, C., and DOUMER, E. L'hypotension orthostatique Press méd., 40: 17, 1932.

56 [illegible]

Brožek, J., Chapman, C. B., and Keys, A., J. Amer. med. Ass., 137: 1569, 1948

57 LEYTON, G. B. Effects of slow starvation. Lancet, 2. 73, 1946.

58 LUFT, R., and VON EULER, U. S. Two cases of postural hypotension showing a deficiency in release of nor-epinephrine and epinephrine J. clin. Invest., 32: 1065, 1953.

59 [illegible]

60 MACLEAN, A. R., ALLEN, E. V., and MAGARTH, T. B. Orthostatic tachycardia and orthostatic hypotension; defects in return of venous blood to heart Amer Heart. J., 27: 145, 1944.

61 McMICHAEL, J., and SHARPEY-SCHAFER, E. P. Cardiac output in man by direct Fick method, effects of posture, venous pressure change, atropine, and adrenaline Brit Heart J., 6: 33, 1944

62 MACWILLIAM, J. A. Blood pressure and heart action in sleep and dreams — Their relation to haemorrhages, angina and sudden death Brit. med. J., 2. 1196, 1923

63 MADDOCK, W. G., and COLLER, F. A. Peripheral vasoconstriction by tobacco and its relation to thrombo-angitis obliterans. Ann Surg., 98. 70, 1933

64 MATHERS, J. A. L., PATTERSON, M. C., and LEVY, R. L. Some effects on the circulation of smoking cigarettes with varying nicotine content. Amer Heart J., 37 612, 1949

65 MAY, H. Das Verhalten der Blutdruckamplitude während des Essens bei gesundem und kranken Kreislauf Med Klin., 25: 829, 1929

66 MECHELKE, K., and NUSSER, E. Circulatory alterations in the Müller experiment Z. Kreisl.Forsch., 42 842, 1953

67 MÜLLER, C. Die Messung des Blutdrucks am Schlafenden als klinische Methode speciell bei der gutartigen (primären) [illegible]

68 [illegible]

69 NORRIS, A. H., SHOCK, N. W., and YIENGST, M. J. Age changes in heart rate and blood pressure responses to tilting and standardized exercise Circulation (N.Y.), 8. 521, 1953

70 OLIVER, S., Studies in blood pressure Lewis & Co., London, 1916.

71 PRICE, H. L., CONNER, E. H., ELDER, J. D., and DRIPPS, R. D. Effect of sodium thiopental on circulatory response to positive pressure inflation of lung J. appl. Physiol., 4 629, 1952.

72 ROSE[illegible] poten-

73 ROY [illegible] 1951. [illegible] 1954, 5th edn. [illegible] and

relationships between intrathoracic, intraspinal, and arterial pressures. J. Amer. med. Ass., **107**: 853, 1936
34 HELWEG-LARSEN, P., HOFFMEYER, H., KIELER, J., THAYSEN, E. H., THAYSEN, J. H., THYGESEN, P., and WULFF, M. H. *Famine disease in German concentration camps. Complications and sequels with special reference to tuberculosis, mental disorders, and social consequences* Acta psychiat. (Kbh.) Suppl. 83, 1952.
35 HICKAM, J. B., and PRYOR, W. W. Cardiac output in postural hypotension J. clin. Invest., **30**. 401, 1951.
36 HILL, L. Arterial pressure in man while sleeping, resting, working, bathing. J Physiol (Lond.), **22**. 26, 1898.
37 HILL, L. On rest, sleep, and work and the concomitant changes in the circulation of the blood. Lancet, *1*: *282*, *1898*.
38 HINES, E A., JR, and ROTH, G M. The effect of tobacco on the blood pressure as measured by a standard smoking test Proc. Mayo Clin., **13**· 524, 1938.
39 HOOD, B., BJÖRK, S., ANGERVALL, G., and RUDBÄCK, H. Muscular exercise in essential hypertension. The effect of hexamethonium chloride (C6) Acta med. scand., **147**. 213, 1953
40 HORST, K., BUXTON, R. E., and ROBINSON, W. D The effect of the habitual use of coffee or decaffeinated coffee upon blood pressure and certain motor reactions of normal young men. J. Pharmacol., **52**: 322, 1934
41 HORST, K., and JENKINS, W. L. The effect of caffeine, coffee and decaffeinated coffee upon blood pressure, pulse rate and simple reaction time of men of various ages J Pharmacol., **53**. 385, 1935
42 HORVATH, S M. *Orthostatic hypotension following hot or cold baths*. Fed Proc., **7**. 57, 1948
43 HOWARTH, S Cardiac output and the peripheral circulation. Special Report No. 275, Medical Research Council, 1951, p 238 His Majesty's Stationery Office, London.
44 HOWELL, W. H. A contribution to the physiology of sleep, based upon plethysmographic experiments J exp Med., **2**: 313, 1897
45 IRVINE, R. O H Unpublished observations.
45a ITAHARA, K., FUKUCHI, S., FUJIBAYASHI, T., and YAMAGUCHI, M Frequency of essential hypertension and the influence of environmental condition thereon Tohoku J. exper Med., **61**. 231, 1955
46 JACOBSON, E Variation of blood pressure with skeletal muscle tension and relaxation II The heart beat Ann intern Med., **13** 1619, 1939
47 KALSER, M. H., FRYE, C W., and GORDON, A S Postural hypotension induced by atropine sulfate Circulation (N Y), **10**· 413, 1954
48 KANZOW, U Beobachtungen während einer 53 tägigen Hungerperiode an einem Hungerkünstler. Dtsch Arch klin Med., **198**. 698, 1951
49 KATSCH, G., and PANSDORF, H Die Schlafbewegung des Blutdrucks. Münch. med. Wschr., **69**· 1715, 1922
50 KEYS, A., BROŽEK, J., HENSCHEL, A., MICKELSEN, O., and TAYLOR, H L. The biology of human starvation Vol II, 1950 University of Minnesota Press, Minneapolis
51 KORNER, P. I The normal human blood pressure during and after exercise, with some related observations on changes in the heart rate and the blood flow in the limbs Aust J exp Biol med Sci., **30** 375, 1952
52 LANDIS, C Changes in blood pressure during sleep as determined by the Erlanger method. Amer. J. Physiol., **73**· 551, 1925.
53 LAPLACE, L. B. *Observations on a case of intermittent postural hypotension* Ann intern. Med., **17**. 339, 1942
54 LAUBRY, C. Leçons de sémiologie cardio-vasculaire. Art. Vertigo, p 339,

## CHAPTER V

# THE CLINICAL MANIFESTATIONS OF HYPERTENSION

The use of the phrase "clinical manifestations of hypertension" assumes that certain clinical manifestations are the result of high blood pressure as such, or of a closely allied phenomenon, such as vasoconstriction. While many hold this view, there are still a few who think that hypertension is a symptom and not the cause of the clinical manifestations which are associated with essential hypertension. Some additional evidence that hypertension may cause or accelerate the clinical conditions referred to in this section is set out in Chapter XI.

## CARDIAC ASTHMA

The term 'cardiac asthma' was first used by James Hope (1842). The condition is probably best defined as paroxysmal dyspnoea of cardiac origin, usually occurring at rest but sometimes caused by exertion The attack may be comparatively mild or of extreme severity. It may last minutes or hours.

### Pathogenesis of Cardiac Asthma

The disorders in which cardiac asthma is encountered have certain features [illegible] ur pulmonary congestion [illegible] Cardiac asthma may be [illegible] high blood pressure, in aortic stenosis and in aortic regurgitation. It may occur from cardiac infarction involving the left ventricle. Cases of cardiac asthma of obscure origin occur from time to time, and some of these may be due to interference with the function of the left ventricle due to diffuse narrowing of the coronary blood vessels or from syphilis of the first part of the aorta, involving the coronary arteries.

Although pulmonary congestion may be apparently more pronounced in mitral stenosis than in some of the above conditions, cardiac asthma is less frequent in mitral stenosis and when it occurs it is commonly after exertion, sexual intercourse, or when tachycardia adds to the work of the heart A possible explanation has been suggested by Dexter (1952), who thinks that constriction of the pulmonary arterioles may be a means whereby the capillary bed of the lung is protected from overdistension. Such an explanation would be

74 ROTH, G. M. Effects of smoking of tobacco on the cardiovascular system of normal persons and patients with hypertension. J. Amer. Geriatrics Soc., 2: 270, 1954.

75 RUSHMER, R. F. Circulatory effects of 3 modifications of Valsalva experiment; experimental survey. Amer. Heart J., 34: 399, 1947.

76 SARNOFF, S. J., HARDENBERGH, E., and WHITTENBERGER, J. L. Mechanism of the arterial pressure response to the Valsalva test; the basis for its use as an indicator of the intactness of the sympathetic out-flow. Amer. J. Physiol., 154: 316, 1948

77 SCHRADER, H. J. *Hypertonie nach Hungerkrankheit. Medizinische*, 41: 1291, 1952.

78 SHARPEY-SCHAFER, E. P. The mechanism of syncope after coughing. Brit. med. J, 2: 860, 1953.

79 SIMONSON, E., and ENZER, N. Physiology of muscular exercise and fatigue in disease. Medicine (Baltimore), 21: 345, 1942.

80 SPIES, T. D., and STONE, R. E Hypotension associated with nutritive failure. Proc. Soc exp. Biol (N Y), 72: 368, 1949

81 STEAD, E. A., JR., and EBERT, R. V. Postural hypotension — A disease of the sympathetic nervous system Arch intern. Med., 67: 546, 1941.

82 STEAD, E. A, JR, WARREN, J V., MERRILL, A. J., and BRANNON, E. S The cardiac output in male subjects as measured by the technique of right arterial catheterization — Normal values with observations on the effect of anxiety and tilting J. clin. Invest., 24: 326, 1945

83 TARCHANOFF, J. Quelques observations sur le sommeil normal. Arch. ital Biol., 21: 318, 1894.

83a TAYLOR, N. B. G., and NOBLE, R. L. Appearance of an antidiuretic substance in the urine of man after various procedures Proc. Soc. exp. Biol, 73. 207, 1950.

84 THACKER, E. A Blood pressure studies on university students, including the effect of exercise on essential hypertension, hypotension and normal subjects. Ann. intern Med, 14 415, 1940

85 THOMPSON, W. G, and SHELDON, W. H. Tobacco smoking and blood pressure N Y St. J. Med, 17: 55, 1917

86 VAQUEZ, M. H. De la tension artérielle pendant la grossesse et les suites de couches Bull. Soc. Obstét Gynéc Paris, 9: 30, 1906.

86a VEREL, D. Postural hypotension: the localization of the lesion Brit. Heart J., 13: 61, 1951.

87 WALLACE, J., and SHARPEY-SCHAFER, E. P Blood changes following controlled haemorrhage in man Lancet, 2. 393, 1941.

87a WHEELER, H. O., WADE, O. L., COMBES, B., CHILDS, A W., COURNAND, A., and BRADLEY, S E. Effect of exercise on splanchnic blood flow and splanchnic blood volume in man Fed Proc, 15: 198, 1956

88 WILKINS, R. W, CULBERTSON, J W., and SMITHWICK, R H. The effects of various types of sympathectomy upon vasopressor responses in hypertensive patients Surg Gynec Obstet, 87: 661, 1948.

89 ZIMMER, R, WEILL, J., and DUBOIS, M The nutritional situation in the camps of the unoccupied zone of France in 1941 and 1942 and its consequences New Engl J Med, 230: 303, 1944

pressure, and decrease in vital capacity during the early hours of the morning.

Halmagyi et al. (1953) found that in sleep there is a decrease in pulmonary artery pressure and in the pulmonary arteriolar resistance. This they think may increase the pressure in the pulmonary capillaries and, together with haemodilution, cause an attack of cardiac asthma.

It seems likely that the attack of cardiac asthma is determined by the occurrence of passive congestion in the lung capillaries and that this is due mainly to disproportionate activity of the two ventricles. Many other factors also must influence the occurrence, such as the blood volume, the state of contraction or relaxation of pulmonary vessels, the colloid osmotic pressures of plasma and of exuded fluid. Anoxia and carbon dioxide retention will have an influence on several of the factors mentioned above.

## Clinical Manifestations of Cardiac Asthma

A first attack of cardiac asthma may be of alarming severity but, not infrequently, the early manifestations are comparatively mild, [illegible] om simple orthopnoea. [illegible] in bed. A patient who [illegible] ssness is awakened by distressed breathing or a sense of suffocation, sits up in bed, perhaps coughs a little, and before long the attack subsides, and the patient can lie flat again. The condition may be provoked by a respiratory or other infection. Attacks are sometimes frequent, even nightly but they do not always warrant an emergency consultation.

The fully developed attacks of cardiac asthma, however, cause patients grave respiratory distress, and alarm the relatives. Most frequently they occur at night, though occasionally there are attacks during the day-time. The patient may be wakened from sleep, or the attack may occur not long after retiring and before the patient has slept.

Distress [illegible] erity the patient is [illegible] the features are cold [illegible] frothy oedema fluid may be coughed up or dribble from the corners of the mouth. The patient uses all accessory respiratory muscles, and sometimes grips the side of the bed to render their action more effective. Often patients find that sitting on the side of the bed with the legs hanging down, or sitting in a chair by the side of the bed is the most tolerable posture. Râles are usually present in the chest, at least at the bases, but often they can be heard over the whole chest. Wheezing noises, such as are encountered in bronchial asthma, may be present to a degree which suggests the latter disorder. They are often audible without a stethoscope. There may be cough and expectoration.

compatible with high pulmonary artery pressure and radiological evidence of congestion, yet with comparatively infrequent occurrence of cardiac asthma and pulmonary oedema. Kilpatrick (1955) has noted increase of breathlessness in cases of mitral stenosis after hexamethonium. This was associated with decrease in the pulmonary artery pressure, which lends some support to the Dexter hypothesis. In contrast, hexamethonium relieves dyspnoea in cardiac asthma due to hypertension.

Cournand (1952) points out that when the left ventricle fails the diastolic filling pressure is increased, and the rise of pressure is transmitted back to the pulmonary circulation. The observations of Weiss and Robb (1933) suggest that in cardiac asthma there is a stagnant engorgement of the lungs with blood and not an active hyperaemia. The resulting rise in the pulmonary capillary pressure above the colloid osmotic pressure of the plasma, increases the effective filtration pressure and favours the outpouring of fluid into the alveoli. Furthermore, in advanced cases, the protein content of the oedema fluid which may be expectorated is between 2 and 4 per cent, indicating a degree of permeability of the blood vessels to proteins. The protein content diminishes the effective colloid osmotic pressure of the plasma in the lung capillaries and is likely to be associated with an increase in the outward transudation of fluid.

Relief of cardiac asthma may occur when the right ventricle also fails and lowers the pulmonary pressure, but this is not invariable, and paroxysmal exacerbations of the dyspnoea may persist, presumably because the degree of failure remains greater in the left than in the right ventricle. Pulmonary congestion is decreased by measures which decrease the blood volume, such as venesection, a salt-poor diet, or a mercurial or other effective diuretic. All these measures lessen the tendency to attacks of cardiac asthma. The sitting posture, and passive venous congestion of the legs by cuffs, both act by diverting blood from the lungs. Late evening meals, nightmares, coughing, and other conditions which may increase the venous return to the heart may precipitate attacks of cardiac asthma. The striking relief of an attack of cardiac asthma which follows the intravenous administration of hexamethonium is probably due in part to decrease in the left ventricular overload, and partly to dilatation of systemic veins and withdrawal of blood from the pulmonary circulation (see ChapterXIX)

While it is comparatively easy to understand why breathlessness should occur in hypertension, it is much harder to explain why the breathlessness should occur paroxysmally and at rest. It was suggested by Brunn (1928) that, on retiring to bed, manifest or latent oedema is absorbed, increasing the blood volume. An observation which supports this hypothesis was made by Perera and Berliner (1943) who noted a decrease in the serum protein concentration, increase in venous

pressure, as ordinarily measured, is the casual blood pressure taken at a clinic minus the basal blood pressure. However, it would be incorrect to assume on this basis that all the changes in the supplemental pressure under daily living conditions are without influence on the development of congestive heart failure).

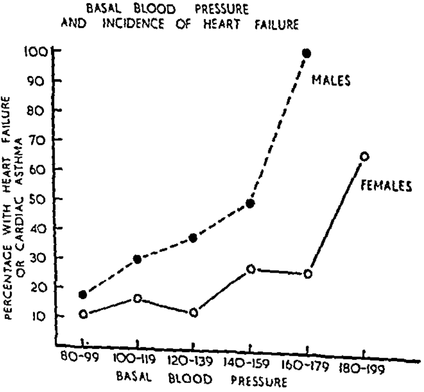



Fig V 1

Relationship of the mean basal blood pressure (basal diastolic + basal systolic)/2 to the percentage incidence of heart failure or cardiac asthma in a series of hypertensive patients

If in a patient with congestive heart failure the blood pressure is very high, say 240/140, there is *usually little* doubt that the heart failure is due mainly to the hypertension. When, however, the blood pressure is in the region of 170/100 it is likely that other factors are concerned also. Such factors as cardiac ischaemia, senile changes, infection, bronchitis, emphysema, obesity and cardiac arrhythmias may be more important than the moderate degree of blood pressure elevation. We have obtained evidence, however, that in many such cases decrease of the cardiac overload, brought about by reducing

### Differential Diagnosis of Cardiac Asthma

This is seldom difficult if the patient has been investigated previously. Sometimes, difficulty arises with patients who have both a raised blood pressure and bronchial asthma, especially where the bronchial asthma is of long duration and associated with some degree of cardiac embarrassment. A response to fractional administration of hexamethonium bromide, intravenously, will be of value, for this seldom is beneficial in bronchial asthma, whereas in cardiac asthma prompt and dramatic relief is usual. Where a patient is seen for the first time in an attack of breathlessness the diagnosis may be difficult, and such alternatives need consideration as bronchial asthma, acute respiratory infection, hysteria or fright associated with hypertension, and pulmonary embolism. In cardiac asthma the colour is seldom as cyanotic as in bronchial asthma. Cottrell and Cuddie (1942) showed that in cardiac asthma the arm to tongue circulation time is prolonged beyond 17 seconds, whereas it is normal in uncomplicated bronchial asthma.

The presence of an enlarged heart with a forcible, thrusting apex beat will be of value. In bronchial asthma the heart will not usually be as large and the impulse, because of emphysema, is less readily felt. The blood pressure will almost certainly be raised in cardiac asthma, although occasionally in extreme cases the blood pressure may fall during the attack.

In hysterical overbreathing associated with hypertension, tetany may be present. Free respiratory movements of wide amplitude do not occur in cardiac asthma. In pulmonary embolism it is not usual to find râles so widely distributed.

## CONGESTIVE HEART FAILURE

### Pathogenesis of Hypertensive Heart Failure

Generalized congestive heart failure is not invariably preceded by attacks of cardiac asthma. Two factors play an important part in the development of hypertensive heart failure and there are several others of secondary importance. First, there is the direct effect of the added work to be performed by the heart. Second, the heart muscle may outgrow its own blood supply and there may be some narrowing of coronary arteries. Hence, with an absolute or relative decrease of its blood supply, the heart may be called upon to do more work.

Among groups of patients with hypertension there is a relationship between the height of the casual blood pressure and the occurrence of congestive failure. We find [77] a strong correlation between the height of the mean basal blood pressure (diastolic plus ½ pulse pressure), and the incidence of congestive heart failure (Fig. V 1) and little or no relationship with the height of the supplemental pressure as ordinarily measured. (Attention is drawn to the fact that the supplemental

Evans and White (1948), however, were not convinced that a syndrome of this kind occurs. Certainly, among hypertensive patients there are examples of neck vein engorgement, dependent oedema and liver enlargement which are unaccompanied by râles or x-ray evidence of pulmonary congestion.

## Sodium Retention as a Factor in Congestive Heart Failure

It has long been recognized that fluid retention accentuates and loss of fluid from the body ameliorates the symptoms of congestive heart failure Retention and excretion of fluid is to a large extent determined by the excretion or [illegible] such as those used by Kempner [illegible] heart failure partly because the[illegible] lower the blood pressure but also because they decrease the amount of fluid retention.

The mechanism by which sodium is retained in the body has been widely discussed but is not necessarily due to the operation of a single process. It has been [illegible] of [illegible] us [illegible] dr [illegible] sarily [illegible] with c[illegible] increa[illegible] in par[illegible] changes in the developed state of congestive heart failure there are several changes which promote a movement of fluid from the plasma to the tissue spaces (Smirk, 1936) The colloid osmotic pressure of the plasma is somewhat decreased, the permeability of capillaries to water and salts is increased, the general venous pressure is increased and the local venous pressure in dependent limbs is increased because the pumping action of muscles on veins is [illegible] has accumulated in the [illegible] the stimulus to the renal [illegible] VI)

## Clinical Features of Congestive Heart Failure in Hypertension

The clinical features of hypertensive heart failure are familiar: breathlessness on exertion and later at rest, is accompanied by orthopnoea and in some cases by Cheyne-Stokes breathing. Oedema is present in dependent parts and râles are usually heard at the lung bases, the liver is enlarged and there may be ascites. The apex beat is usually of a thrusting character, commonly found in the sixth space and well outside the mid-clavicular line. There will usually be an apical systolic murmur and the aortic second sound is accentuated. Exceptionally a "functional" aortic regurgitant murmur is present due presumably to dilatation of the valve ring. We have, on occasion, confirmed the absence of organic valve changes in such a case, at autopsy. The onset of congestive heart failure is often preceded by

the blood pressure to strictly normotensive levels, may be distinctly beneficial even when heart failure is due mainly to other causes.

Patients with hypertension, not exhibiting congestive failure or obvious cardiac embarrassment, have either a normal or only slightly reduced cardiac output (Burwell and Smith, 1929; Goldring and Chasis, 1944). *There is good evidence that in hypertensive heart failure the* cardiac output is usually decreased (Cournand, 1952).

Ordinarily the heart is capable of a great increase in its output without appreciable dilatation, whereas if dilatation is necessary in order to maintain the output, a serious impairment in the heart capacity has already taken place. In congestive failure the cardiac output represents an almost maximal effort on the part of a heart which, in order to perform that effort, has utilized its available reserves. *Although dilatation of the heart represents a compensatory* process, its presence is of adverse significance.

Increase in the peripheral resistance causing mechanical overloading of the heart is probably *the most important single factor* responsible for heart failure in hypertension. Certainly, in some patients, there is evidence that hypertension has been associated with irreversible damage of the heart, but the great majority of patients benefit from reduction of the blood pressure level by methonium salts The effect of treatment with ganglion blocking drugs is not as dramatic in patients with general congestive heart *failure as in left* ventricular failure with cardiac asthma; nevertheless, most patients *with general congestive heart failure recover to a stage of climbing* 20 or 30 steps, without the assistance of digitalis, salt restriction or mercurial diuretics.

Treatment with hexamethonium by injection does not remove the load of peripheral resistance from the heart for the whole of the 24-hour day and probably, with three injections, effective blood pressure reduction is of 9 or 10 hours' duration only, yet this leads to recovery of function It seems likely, therefore, that the mechanism of the heart is such that it tolerates intermittent loads fairly well, but is less well able to tolerate continuous loads, such as are imposed when a patient has a high basal as well as a high supplemental blood pressure.

## Bernheim's Syndrome in Hypertension

Bernheim (1910) made the suggestion that *bulging of the septum* of an enlarged *left ventricle into the cavity of the right ventricle* might interfere with right ventricular filling and cause systemic venous congestion. Bernheim noted that, in his cases, the systemic congestion was not accompanied by evidence of pulmonary engorgement. Atlas et al. (1950) and Russek and Zohman (1950) have reported examples of what they took to be Bernheim's syndrome.

## OTHER CIRCULATORY MANIFESTATIONS

### Simple Breathlessness on Exertion

Many patients with high blood pressure exhibit symptoms of breathlessness on exertion and may use an extra pillow at night, but otherwise feel substantially well and be comfortable at rest. Probably the changes which ultimately lead to congestive heart failure are operating to a smaller degree. In many cases, however, some breathlessness is present without the suggestion either clinically or radiologically of pulmonary congestion. A purely speculative explanation is that a left ventricle capable of handling normal or slightly raised cardiac outputs, experiences difficulty in the onward movements of larger blood volumes. Pulmonary congestion may be a temporary phenomenon. Breathlessness on exertion short of congestive heart failure is relieved in a great majority of patients by effective methonium treatment. It seems likely that the decrease of the load on the left ventricle has been responsible for the relief.

### Cardiac Enlargement

It is well known that some patients who have had a high blood pressure for perhaps 5, 10 or even 15 years may show little change in the size of the heart. When cardiac hypertrophy occurs it appears to be due to an increase in the thickness, but not in the number, of heart muscle fibres. Weiss et al (1936) and Kleinfeld and Redish (1952) have expressed the view that there is no simple correlation between cardiac hypertrophy and the height or duration of the hypertension Stein and Barnes (1948) in a series of 111 cases noted that the degree of hypertrophy seemed to be directly related to the severity group of the hypertension but not to the duration of hypertension. We have found in our clinic a rough correspondence between the height of the casual blood pressure and the size of the heart but a closer correspondence between basal blood pressure and heart size. A close relationship between the casual blood pressure and the heart size is not to be expected for two reasons:

First, in a proportion of patients who show no cardiac enlargement the blood pressure may be labile and elevated only at times of physical activity or emotional tension. We have found that there is a strong correlation between the level of the mean basal blood pressure and the presence of cardiac enlargement (Fig V 2) but the level of the supplemental pressure is unrelated to the size of the heart. Possibly some of the hypertensive patients who have withstood high blood pressure for a long period of time are patients whose blood pressure only recently has become elevated continuously.

Secondly, some patients will have concentric hypertrophy of the cardiac muscle, but comparatively little change in the cardiac sil-

accentuation of the pulmonary second sound which may be louder than the aortic second sound. This is due to a rise of pressure in the pulmonary circulation. Pulmonary congestion may be suggested clinically, and can be confirmed radiologically. Often pleural effusion is present, sometimes obvious at physical examination and sometimes requiring a radiographic diagnosis. Pulmonary congestion may be associated with cough and, on occasion, with haemoptysis. Cyanosis is not uncommon terminally.

In most patients with hypertensive heart failure the blood pressure is maintained at a high level. Indeed, in some patients the blood pressure falls almost to normal levels when the heart failure is relieved by digitalis. The phenomenon was called Hochdruckstauung (high pressure stasis) by Sahli (1901).

Electrocardiograms almost always show hypertensive changes before heart failure develops. The presence or absence of failure (apart from the action of digitalis) makes no striking change. Almost invariably, however, with continued blood pressure reduction the electrocardiographic picture improves, though sometimes only to a slight degree.

Cardiac delirium occurs in a proportion of cases, especially in elderly individuals. It is mainly nocturnal but there may be some disorientation during the daytime. The patient may be uncertain of his location, or of whether he has been visited by the doctor or by his relatives. A tendency to get out of bed and wander at night occurs in hypertensive heart failure as in other types. Sometimes this delirium occurs in convalescent patients who have recovered from the failure.

## Comment

Cardiac asthma, congestive heart failure or simple breathlessness on exertion may occur as clinical manifestations in hypertension from all causes. Before the introduction of hypotensive therapy, congestive heart failure was the commonest cause of death in cases of hypertension without serious renal involvement. At the present time the outlook in cases of cardiac asthma and congestive heart failure is good, for at least several years, and probably for a much longer period of time. Evidence will be presented later that, with adequate treatment, deaths from hypertensive heart failure should be most exceptional unless some additional factor, such as cardiac infarction, or renal insufficiency, has caused damage to the myocardium. I am therefore led to believe that there may have been a tendency in the past to overemphasize the part played by permanent pathological changes in the myocardium, and to pay insufficient attention to the effects of long lasting overload on one or both ventricles. There is some evidence that an intermittent overload is better tolerated by the heart than a constant overload.

## OTHER CIRCULATORY MANIFESTATIONS

### Simple Breathlessness on Exertion

Many patients with high blood pressure exhibit symptoms of breathlessness on exertion and may use an extra pillow at night, but otherwise feel substantially well and be comfortable at rest. Probably the changes which ultimately lead to congestive heart failure are operating to a smaller degree. In many cases, however, some breathlessness is present without the suggestion either clinically or radiologically of pulmonary congestion. A purely speculative explanation is that a left ventricle capable of handling normal or slightly [illegible]

[illegible] failure is relieved in a great majority of patients by effective methonium treatment. It seems likely that the decrease of the load on the left ventricle has been responsible for the relief.

### Cardiac Enlargement

It is well known that some patients who have had a high blood pressure for perhaps 5, 10 or even 15 years may show little change in the size of the heart. When cardiac hypertrophy occurs it appears to be due to an increase in the thickness, but not in the number, of heart muscle fibres. Weiss et al. (1936) and Kleinfeld and Redish (1952) have expressed the view that there is no simple correlation between cardiac hypertrophy and the height or duration of the hypertension. Stein and Barnes (1948) in a series of 111 cases noted that the degree of hypertrophy seemed to be directly related to the severity group of the hyper[illegible]

[illegible] and the size of the heart but a closer correspondence between basal blood pressure and heart size. A close relationship between the casual blood pressure and the heart size is not to be expected for two reasons

First, in a *proportion of patients* who show [illegible] the blood [illegible] ac[illegible] co[illegible] mean basal blood pressure and the presence of cardiac enlargement (Fig V 2) but the level of the supplemental pressure is unrelated to the size of the heart. Possibly some of the hypertensive patients who have withstood high blood pressure for a long period of time are patients whose blood pressure only recently has become elevated continuously.

Secondly, *some* patients will have concentric hypertrophy of the cardiac muscle, but comparatively little change in the cardiac sil-

houette. Radiographic evidence of a normal silhouette does not eliminate the possibility or even the probability of cardiac hypertrophy. The palpation of a forcible, thrusting apex beat, often felt just outside the mid-clavicular line would seem to be suggestive of cardiac hypertrophy even when the cardiac silhouette is normal.

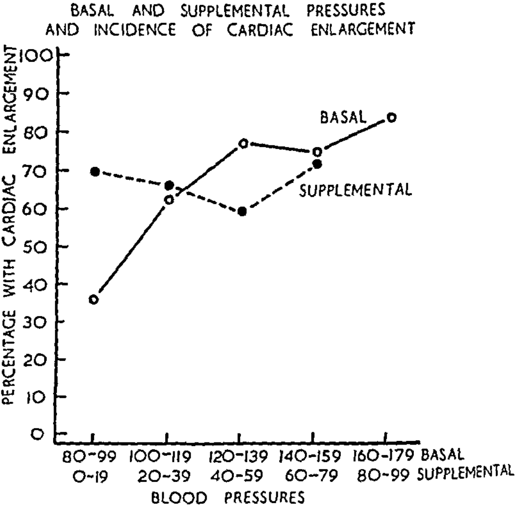



Fig V 2

Relationship of the mean basal blood pressure (basal diastolic + basal systolic)/2 and the mean supplemental pressure (supplemental diastolic + supplemental systolic)/2 to the percentage incidence of cardiac enlargement in a series of hypertensive patients

Increased voltage in the left venticular leads of the electrocardiogram, often with T wave inversion or ST segment depression, provides a degree of confirmation.

In patients where a degree of cardiac enlargement exists, confirmation that the left ventricle is involved particularly may be obtained in a left anterior oblique view. In this view when the patient is rotated through an angle of 55° the shadow of the apex of the left ventricle may be seen to overlap to some extent the shadow of the thoracic vertebral bodies when the left ventricle

s enlarged. The degree to which the patient must approximate to a full lateral position before a clear gap is seen between the left ventricle and the vertebral bodies provides an indication of the degree of left ventricular enlargement. In some instances the left ventricle overlaps the vertebral bodies in a full left lateral position. Even when there is no increase in the area of the ...

which overlaps the heart shadow is longer in the hypertensive than in the normotensive. While this is not an invariable guide to cardiac hypertrophy it is a common feature. When failure has developed, enlargement involves both the left and right side of the heart and congestive changes make their appearance in the lungs.

A decrease in heart size is to be expected if heart failure is relieved, by whatever means. In view of the ... to the size of the cardiac silho... concerning congestive heart fa... ...been built around Starling's observations relating strength of heart contraction to ...

... that had the cardiac shadow obtained in the horizontal posture been obtained with the patient in the standing posture, increase in the heart size would have been diagnosed confidently.

There is not general agreement about the relationship between coronary narrowing and hypertrophy of the heart. Clawson (1939) in a study of 928 cases of coronary sclerosis came to the conclusion that there was no evidence to support the claim that cardiac hypertrophy results from coronary sclerosis. He thought hypertension was the most common associated condition. Most writers, however, think that cardiac enlargement is due sometimes to coronary artery narrowing. Master (1954) in a recent study of the relationship between cardiac enlargement, hypertension and coronary disease, points out that coronary disease alone may cause cardiac enlargement, but is particularly likely to do so when associated with blood pressure elevation.

## Electrocardiographic Changes

The electr...

m...

ex... to a left ventricular overload, and those which are indirectly related or may be unrelated ...

cy...

fl...

w...

... Some of the changes which occur in

the electrocardiograms of hypertensive patients have been ascribed to ischaemia of heart muscle, brought about by cardiac hypertrophy or narrowing of the coronary arteries, or both. The possibility of reversing

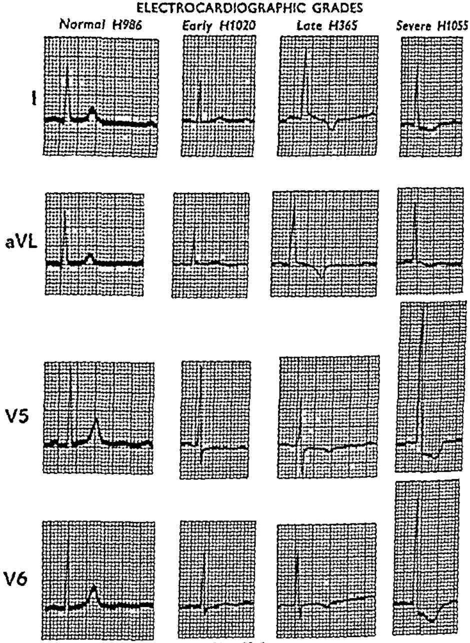



Fig V 3

*Examples of hypertensive changes in the electrocardiogram of early, late and severe grades.*

electrocardiographic changes to some extent, and occasionally completely, by continued blood pressure reduction (Smirk and Alstad, 1951; Doyle, 1953) indicates that they are not all due to permanent changes in the cardiac muscle or its blood supply.

The characteristic hypertensive changes to which reference is made have been described by a number of authors [29, 30] and are as follows: (Fig. V 3). In the bipolar limb leads the R wave is commonly high in lead 1 and the S wave deep in lead 3, partly the result of left ventricular hypertrophy and partly due to a more horizontal electrical axis. In the early stages there may be no alterations in the T waves or ST segment. In the course of time the T wave diminishes in voltage in lead 1, may become iso-electric, biphasic, or undergo a clear inversion. A fall in the ST segment accompanies the T wave inversion in lead 1 in advanced cases. In the third limb lead the T wave usually remains positive, the ST segment may be slightly elevated.

In the unipolar limb leads the changes which have been described for lead 1 are commonly found in the left arm lead, $aV_L$, as the electrical axis of the heart is usually horizontal. Exceptionally, the electrical axis of the heart may be vertical, most usually from a vertical position of the heart, and in such cases the increased voltage of the R wave, inversion of the T wave, depression of the ST segment, may [illegible]

[illegible] rotation of the heart. Leads over the left ventricle exhibit increased height of the R wave. The T wave first decreases in voltage, becomes biphasic or iso-electric [illegible]
with a depressio[illegible]
chest leads 1, 2 [illegible]
to show deep S waves, increased height of the T wave and elevation of the ST segment The phenomena which have been responsible for the changes in positions 5 and 6 are seen in positions 1, 2 and 3, but in reversed polarity.

Bechgaard (1949) found a much greater mortality when the electrocardiogram was abnormal. Of 753 patients with a normal electrocardiogram, 591 were alive and 162 dead, but of 137 with an abnormal electrocardiogram only 54 were alive and 83 were dead.

## Gallop Rhythm

Gallop rhythms are usually present in hypertensive heart failure, or in patients with breathlessness short of failure The gallop may be presystolic or protodiastolic. Occasionally a quadruple gallop rhythm is heard Observations made here by Miles (1951) with simultaneous records of venous pressures, electrocardiograms and heart sound tracings indicate that the presystolic gallop rhythm is heard more frequently than the protodiastolic in hypertension and that the prognostic significance of a gallop is less definite than has been supposed Gallops often disappear with continued blood pressure reduction (Smirk and Alstad, 1951).

## Pulsus Alternans

*Pulsus alternans* is best detected by the sphygmomanometer and may be present with differences of 5 to 20 mm. Hg between the alternate systolic pressures. Alternation may precede congestive heart failure, and may be present during failure. Alternation disappears with continued blood pressure reduction (Smirk et al., 1956) and sometimes even in an acute experiment when the blood pressure level is reduced by hexamethonium.

## Palpitation

Palpitation is, by repute, one of those symptoms which directs attention as much to the reactions of the patient's mind as to the activity of the circulatory system. The extent to which the heart's action reaches consciousness is closely related to the presence or absence of those qualities of mind which determine the disposition of the patient to "psychoneurotic" exaggeration or initiation of symptoms. There is, however, a risk of overlooking the organic basis of an altered heart action which, reaching consciousness, may induce perturbation and anxiety in patients who are prone to these reactions. The beating of the hypertrophied heart is more vigorous and forceful and may be perceptible to the patient as an intrathoracic sensation, even in the absence of any cardiac arrhythmia or tachycardia. In a proportion of patients premature systoles occur which are more productive of queer chest sensations, in that they are exhibited by hypertrophied hearts. The fact that palpitations disappear in a considerable majority of patients on effective hypotensive treatment, suggests that the presence of hypertrophy of the myocardium, and the fact that the heart is working against a strong peripheral resistance, are important components in the production of the symptom.

## Angina

In men, angina of effort often occurs in the absence of hypertension; but in women both angina and cardiac infarction are much less frequent, and when they occur they are frequently found to be associated with a high blood pressure. It is often assumed that this latter is due to the accelerated development of arteriosclerotic processes in the coronary vessels.

In a series of patients with malignant hypertension referred to by Schottstaedt and Sokolow (1953) the proportion with angina was as high as 20 per cent. Davis and Klainer (1940a) found severe arteriosclerosis of the coronary vessels was 76 per cent greater in essential hypertension than in normotension. Goldstein et al. (1956) found that hypertension was 4.75 times more frequent among females with coronary occlusion than among females without this disease.

In 450 of our patients treated for hypertension, mostly severe, 50 had

angina pectoris and 10 cardiac infarctions. Thus approximately 13 per cent had manifest coronary disease.

It seems very likely that the inter-relationship between hypertension and angina is not restricted to the acceleration of arteriosclerotic processes. There is much evidence that the additional cardiac load which is present in hypertension may lead to angina, even when the degree of coronary arteriosclerosis is of minimal degree, and that angina may develop prematurely in patients with moderate narrowing of the coronary blood vessels.

Blumgart et al. (1940) and Davis and Klainer (1940b) found that some patients with clear cut angina had relatively little coronary disease. They attributed the angina to myocardial hypertrophy. In some instances angina was associated with hypertrophy due to valvular disease. Harrison and Wood (1949) found that in many hypertensive patients the coronary vessels were dilated rather than narrowed. *Doyle* and *Kilpatrick* (1954) noted the absence of significant coronary disease in some of our hypertensive patients with angina who had died from cerebral accidents.

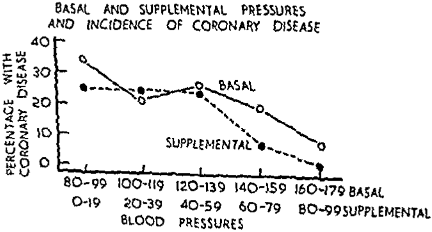



Fig V 4

Relationship of the [illegible] + basal systolic)/2 [illegible] supplemental systolic)/2

[illegible] normal ratio of cardiac work to coronary blood [illegible]
in patients [illegible]
cardia[illegible]
reduct[illegible]
[illegible]

[illegible], of interest that the incidence of coronary disease in our series of hypertensive patients was lower in the patients with high basal pressures and also in patients with high supplemental pressures

(Fig. V 4). It may be that hypertension favours the development of coronary disease but coronary disease interferes with the ability of the circulatory system to maintain a high blood pressure.

## HYPERTENSIVE ENCEPHALOPATHY

The above term was introduced by Oppenheimer and Fishberg (1928). Fishberg (1954) describes the condition as being brought about by disturbances of the brain circulation of two kinds. The first is attributed to cerebral oedema, in which the clinical picture is dominated by manifestations of increased intracranial tension. The second is thought to be the result of cerebral vasoconstriction, with a clinical picture of evanescent cerebral phenomena such as faintness, convulsions, transient paralysis or aphasia. Pickering (1950), however, *found that many patients who had complained of cerebral attacks of* a transitory nature in life exhibited pathological changes in the brain which seemed to provide better explanations of the episodes than spasm or oedema. Some of these episodes occurred in patients with mitral stenosis and auricular fibrillation and were presumably of embolic origin.

It is well recognized that many patients with hypertension exhibit alterations of cerebral function which are of short duration. For example, there may be sudden loss of consciousness accompanied by *no manifest paralysis and, on recovery of consciousness,* no motor or sensory disturbance. Such an attack may occur without warning and may last a few minutes or be of several hours' duration. Often there are no residual manifestations but complete recovery may take several days. Sometimes a cerebral impairment such as aphasia, hemiparesis, or hemianaesthesia, may develop and recover almost completely within one or two hours; but sometimes a day or two may pass before the function is fully restored. Almost any kind of change in the central nervous system function may, theoretically, occur in the form of a brief encephalopathic episode.

It must be accepted, from the occurrence of numerous well documented examples, that cerebral haemorrhage, thrombosis and embolism sometimes cause transient episodes of cerebral dysfunction Cerebral episodes occur also which are unlikely to be due to irreversible changes in the nervous system yet, in the character and duration of their manifestations, they do not differ from the transient disabilities which may occur with organic brain lesions. An example of the latter is the type of cerebral episode which may occur in some patients during excessive lowering of blood pressure induced by methonium salts or by veratrum alkaloids, with rapid recovery soon after the blood pressure is re-elevated. We have encountered hemiparesis, hemiparaesthesia, aphasia and temporary mental disorientation without loss of consciousness. The time taken for partial recovery is brief, and for

ll recovery may be a few hours. The occurrence would appear to be ue to local cerebral ischaemia. Presumably the area of the brain nvolved is supplied by vessels of a calibre which provides an adequate lood supply when the blood pressure is at a high or normal level, ut which becomes insufficient when the blood pressure is at a subormal level. The occurrence in some patients of ophthalmoplegia, phasia or hemianaesthesia, repeatedly, in attacks of migraine, are also favourable to such explanations as cerebral vascular spasm or cerebral oedema Raynaud (1862), in describing the condition named after him, noted paroxysmal loss of sight in association with spasm of the retinal arteries; and Osler (1896) recorded transient cerebral manifestations in the same disorder. There seems no reason to doubt that transient disturbances of cerebral function may be due either to structural lesions in the brain, or to temporary interference with the blood supply of the brain, as from vasospasm or oedema. The question, however, is not whether oedema of the brain or vasospasm occur and cause nervous manifestations, but whether they occur in hypertension.

In hypertensive patients a temporary but extensive interference with cerebral function, is usually diagnosed as an encephalopathy because of the difficulty in believing that an extensive lesion could be due to thrombosis or haemorrhage and yet cause no obvious permanent damage. Such a conclusion however, may not always be justified, for it fails to take account of the possibility that, in thrombosis or haemorrhage, the centre of the lesion may be in a "silent area" of the brain, and the [illegible] only indirectly as [illegible] Consequently wh[illegible] secondary changes at the periphery of the main lesion disappear there may be no detectable residual damage.

Such an explanation, however, may not be satisfactory for very brief episodes, and the repeated occurrence of minor episodes all of very short duration and [illegible] uncommon in hypertens[illegible] think it is likely that som[illegible] attacks represent the occurrence of a temporary and reversible condition rather than a haemorrhage or thrombosis

A beautiful experimental demonstration in the rat of the relationship between severe "Goldblatt" hypertension and the occurrence of "encephalopathic episodes" has been provided by the work of Byrom (1954) In serial sections of 196 brains of rats with encephalopathy, Byrom found major haemorrhages in 22 per cent, capillary haemorrhages in 31 per cent, focal arterial necrosis in 26 per cent, recent infarction in 21 per cent and old infarct[illegible] lesion was seen in 45 per [illegible] tional changes in blood ve[illegible]

ted by a special technique. Using moulded windows of acrylic resin inserted into the skull, Byrom demonstrated spasm of cerebral blood vessels in almost all encephalopathic rats. When the blood pressure was reduced by relief of renal ischaemia the spasm of cerebral vessels was relieved. Using intravenous injections of trypan blue, Byrom was able to demonstrate staining of brain tissues with a patchy distribution. These stained parts were found to show up areas with regional cerebral oedema.

### Blackouts

It is uncertain whether there is any clear distinction except in degree between the phenomenon described as "blackout" and the encephalopathic attack. It is possible that some blackouts might be the result of a temporary disturbance in the blood supply of the retina rather than a cerebral phenomenon. Ordinarily blackouts are of short duration, the milder examples being similar to the postural faintness with momentary darkening of vision which may occur in normotensive individuals more especially when convalescent or unfit, and in response to a sudden change to the erect posture. Blackouts occur more frequently in hypertensive than in normotensive individuals and patients not especially susceptible commonly find that they occur only in response to a change in posture or to stooping. In some patients, however, a blackout may occur without change of posture, there being a darkening of vision, sometimes loss of vision, for one or several minutes. As a rule there is no important disturbance in consciousness and the condition is unassociated with loss of power or tingling sensations in limbs. Attacks cease when effective hypotensive therapy is undertaken.

### Comment

It seems to the author that transient cerebral dysfunction in hypertension may result from various combinations of structural and functional interference with the cerebral circulation. It has been mentioned already that when hypotension is induced in certain hypertensive patients, a brief cerebral dysfunction occurs which resembles a spontaneous encephalopathic episode. It may be presumed in such cases that certain areas of the brain have a blood supply which is marginal but maintains normal function. It is not unreasonable to believe that a general cerebral vasoconstriction, not necessarily of great intensity, might cause symptoms referable to the area with an impaired circulation. It is even possible that vasoconstriction might be sufficient to cause lasting impairment, even with loss of brain substance and cyst formation.

Episodes of local spasm in cerebral vessels are not unlikely. I am informed by our senior neurosurgeon, Mr. James, that spasm of major cerebral vessels may be seen when they are handled in the course of

neurosurgical operations. There is evidence of spasm of neighbouring parts of major limb arteries when they are the site of emboli [1]. It is possible that local vasospasm may occur as the result of a pathological change in a vessel wall which, however, has not led to occlusion. The observations of Byrom (1954) show clearly that encephalopathy may result from cerebral oedema, with a patchy distribution. Evidently temporary interference with cerebral functions can be induced in many ways It seems unlikely that any single explanation will serve to explain all encephalopathic episodes.

## RETINAL CHANGES

Richard Bright was familiar with the visual disturbances associated with renal disease, and it would be interesting to know if he used the ophthalmoscope, which was invented by Helmholtz six years before Bright's death in 1857.

Keith, Wagener and Barker (1939) made a classification of the retinal changes in arterial hypertension which has proved to be of the greatest value, more particularly as a guide to the severity of the disorder and to prognosis. Grades 1 to 4, as set out below, are in ascending order of severity and approximate to the grading suggested by Keith and his co-workers

*Grade* 1. — changes are minimal and consist of mild narrowing of the small arteries and arterioles

*Grade* 2. — involves more advanced retinal vascular changes but no exudative phenomena. The changes are as follows: In the arteries there occur irregularities in the calibre of the vessels such that, when the changes are marked, waist-like deformities may be seen in one or other small artery In addition, as arteries cross veins, the veins may appear to narrow at the point of intersection, an appearance referred to as compression or "nipping" of the arteriovenous crossings. These are the most characteristic changes.

Close observation reveals that there are several kinds of change which contribute to this appearance of compression at the arterio-venous crossings. Actual compression of the vein by the artery may occur. This is sometimes accompanied by banking up of blood in the vein distal to the obstruction. The vein may be displaced *forwards* when the artery crosses it behind or backwards if it crosses *in front*. A degree of opacity of the artery wall may cause concealment of the vein. Normally the red column of blood in the artery renders the underlying vein invisible but the arterial wall is translucent and the venous column is seen through it. When, however, the artery wall is opaque, the venous column cannot be seen *through* it and consequently seems [illegible]

blood [illegible]

for a [illegible] arteriovenous nicking to be recorded.

*Grade 3.* — changes are characteristically exudative. They may occur with or without Grade 2 changes, but usually Grade 2 changes will be present also. Grade 3 changes refer to the presence of haemorrhages, soft exudate or hard exudate, or oedema of the retina. The haemorrhages may be flame-shaped or striate and are often multiple. Sometimes a large haemorrhage takes place with loss of function of part of the retina and a visual field defect. Haemorrhage may be extensive and may cause considerable reduction of vision, from which however there are, sometimes, surprising recoveries Soft exudate is often described as "cotton-wool" exudate. This white exudate has a soft fluffy edge and occurs in small patches, in size often equivalent to about a fifth or a fourth of an optic disc diameter. Hard exudate usually occurs in sharply defined dots which are brighter in appearance than the soft exudate, and the dots of exudate may be very numerous. Exudate may be found anywhere in the retina, but usually is in larger amounts near to the optic discs, and more particularly to the temporal side of the disc, where the white spots of hard exudate may be radially arranged, giving rise to what is called a "star-shaped macular figure". The hard exudate may be considerable in amount and at such times is usually accompanied by some soft exudate, so that in fact much of the retina near to the disc may be occupied by retinal deposits and often oedema.

It is sometimes stated that the appearance of hard and soft exudate indicates involvement of the kidneys. It is not infrequent for a degree of impairment of the renal function to be encountered in patients with much retinal exudate, but this is by no means invariable. The term "albuminuric retinitis", often applied to Grade 3 changes with exudates, is not well chosen, as albuminuria is frequently absent. In the South Island of New Zealand where advanced chronic nephritis is uncommon the majority of our severe hypertensive patients with retinal exudates have normal renal functions, and no albuminuria.

Oedema of the retina without protrusion of the optic disc is a Grade 3 change. It usually occurs principally near the optic disc, but may be more pronounced to one side or another. It is recognized by the fact that the retinal blood vessels are obscured and seen less distinctly as through ground glass, being partially buried in oedematous retinal tissue. Usually retinal oedema is accompanied by other Grade 3 changes.

*Grade 3 to 4.* — changes: It is comparatively common in our experience to encounter patients with obvious Grade 3 changes but in whom there is considerable difficulty in deciding whether Grade 4 changes are also present. The difficulty comes when oedema involving the retina spreads on to the edge of the disc causing a blurring of its outline, but where the amount of oedema is insufficient to cause a definite swelling of the disc, our impressions have been that such a

change may have a significance intermediate between the classical Grade 3 and Grade 4 changes. One reason for making this suggestion is that frank papilloedema in one eye may be associated with changes of an intermediate magnitude, which we have termed Grade 3 to 4 changes, in the other eye. A further reason is that in the course of methonium treatment cases of frank papilloedema may regress within a month to this intermediate stage but two or more months may elapse before retinal oedema, haemorrhages and soft exudates have all disappeared.

*Grade 4.* — The G[illegible]
the optic disc and [illegible]
that the condition [illegible]
cases are readily recognized. The physiological cup is usually filled up and unrecognizable or clearly shallower than is normal. The retinal blood vessels as they cross the edge of the disc are seen to be lifted to a higher level on the disc than on the surrounding retina. This is more readily and more certainly perceived by observation of the smaller capillary blood vessels. Should there be doubt, observation with the binocular ophthalmoscope will often help to settle the [illegible]

[illegible] ophthalmoscope by observing the arteries in cases of hypertension where no question of papilloedema is in dispute. In general [illegible] are unduly constricted. This may be determined by comparing their calibre with veins of normal dimension.

The Grade 4 changes are commonly, but not invariably, accompanied by haemorrhages or exudates. Not infrequently examples of malignant hypertension are encountered in which the arterial changes are surprisingly slight, apart from the generalized vasoconstriction. Doubtless this occurs because many of the malignant hypertensive patients have comparatively short histories. Leishman (1952) has described mural thickening and thrombosis in retinal arterioles of malignant hypertension patients.

In 1945 C. G [illegible]
give a text to a [illegible]
whether primar[illegible] renal, were dependent firstly on the occurrence of a high blood pressure and secondly on the histological vascular changes in the fundus which succeed the hypertonus. Much of the evidence in the literature for the differentiation between vascular retinopathy and renal retinopathy is vitiated by the fact that many cases regarded as chronic nephritis in the past were in reality cases of primary hypertension. The only true test of the ability of the

ophthalmologist or the physician to distinguish between the retinal pictures of hypertension and nephritis is to ask him to make a diagnosis from observation of the eye-grounds alone. I believe that this is a task impossible of achievement even by the most expert ophthalmologist."

The disappearance of exudative changes and papilloedema in nearly all patients receiving effective hypotensive therapy [22, 75, 76] and with different forms of therapy [40, 57, 71] has made it possible to confirm that the changes are due to the hypertension. Hypotensive therapy is effective in cases of nephritis as well as in essential hypertension and

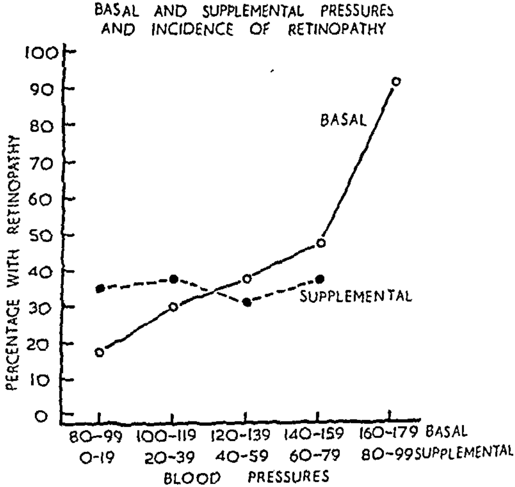



Fig. V 5

Relationship of the mean basal blood pressure (basal diastolic + basal systolic)/2 and the mean supplemental pressure (supplemental diastolic + supplemental systolic)/2 *to the percentage incidence of retinopathy* (grade 2 or more)

nephritic patients whose blood pressures have been reduced may die in uraemia with no exudative changes in the retina. Keith and Wagener (1951) found, however, that in exceptional cases (they saw 15 in 20 years) papilloedema *may subside spontaneously*.

The value of the retinal changes as a guide to the prognosis has

ɜen clearly established by Keith, Wagener and Barker (1939). Fig. II 5 shows their survival curves for the four grades of patients. : will be seen that there is a gradual increase in the steepness of the ırves from Grades 1 to 4. The average survival time of the patients ı Grade 4 was 10.5 months in 146 cases. This figure agrees closely ɩith the observations of most other workers.

There is a close relationship between the height of the mean basal ressure

$$\frac{\text{systolic} + \text{diastolic}}{2}$$

ınd the presence of retinopathy (Fig. V 5) but no relationship etween mean supplemental pressure and retinopathy [77].

*Senile changes* in the small arterial vessels of the retina consist in ıarrowing and straightening, which are probably the result of fibrosis with contraction. Some of the changes encountered in hypertension such as compression of the arteriovenous crossings may occur in elderly people without hypertension, but it may be taken that the changes as a whole are never as numerous nor as marked in senile sclerosis as in prolonged hypertension.

Leatham (1949), who made a careful study of the retinal vessels ın hypertensives and in elderly normotensives, stated that hypertension could be diagnosed with reasonable confidence on ophthalmoscopic findings alone on one of the following criteria:

1. "Irregularity of lumen in at least two arterioles.
2. [illegible] eration in the [illegible] npanion veins, [illegible] the diagnosis [illegible] hypertension at least one retinal arteriole should be half the width of its companion vein with less than the normal two to three ratio between most of the others.
3. Pallor of the arteriolar blood column, arterio-venous crossing changes, and a broad or bright light streak. Of these three changes, at least two must be seen for the diagnosis of hypertension"

## HEADACHE

Headache is a frequent symptom in hypertension. The character of the pain varies considerably: the most characteristic pattern being a morning headache which clears when the patient has been out of bed for a few hours. These morning headaches often may be alleviated by sleeping with the head raised (Maclean and Allen, 1941). The occipital site for hypertensive headaches is only encountered a little more frequently than other locations. The headaches may occur regularly every day, there may be a few headaches a week or severe

bouts of headaches may occur every few weeks. The headache is sometimes associated with vomiting.

Headaches occurring in hypertensive patients are not all due to the hypertension; but the hypertension appears to modify or influence the headaches for almost all of them disappear or are much improved by reduction of the blood pressure. Many patients give a history of migraine early in life, long before the onset of hypertension. In renal and in malignant hypertension the headache may be associated with raised cerebrospinal fluid pressure and increased intracranial tension. They may be prominent in patients who are in a pre-uraemic or uraemic state. Severe headaches may occur in conjunction with encephalopathy and crises of blood pressure elevation. On occasion severe headaches, extending over some days, have been proved to be due to a small cerebral haemorrhage, and it is possible that occasionally these may occur in areas of the brain which give rise to no paralysis or sensory disturbance. Headaches occur, however, in patients who have no evidence of any of these conditions.

Wolff (1948) attributes the headaches in hypertension to dilatation and distension of carotid artery branches. Some other hypertensive headaches he attributes to sustained contractions of the skeletal muscles of the head and neck. He also lays stress upon the occurrence of emotional situations.

Some headaches are evidently due to reversible vascular phenomena. This was demonstrated dramatically in two patients who, while under the action of hexamethonium, noted that the headaches disappeared rapidly on standing and reappeared when they sat down This was tested many times with the same result. When standing the blood pressure was lower in each instance than when sitting.

In some instances the origin of the headache is psychogenic. Hypertensive headaches seem especially liable to develop during states of emotional tension, stress or worry. The suggestion has been made that some of these headaches may be explained, as those of migraine have been explained, by emotional conflicts concerning hostile impulses. It should not be overlooked that states of emotional tension are likely to be associated with rises of blood pressure, whereas reassurance and placebos lead to decreases of blood pressure Some psychogenic headaches may be caused by rises of blood pressure which are of emotional origin, but the relationship between headache and the blood pressure level is inconstant. Some patients with very high blood pressures, as Stewart (1953) points out, do not experience headache until they learn about their hypertension

## OTHER CLINICAL MANIFESTATIONS

### Dizzy Attacks and Vertigo

In the minds of most patients dizzy attacks appear to be clearly

separable from blackouts and encephalopathic attacks. Dizzy attacks, occurring without any definite sensation of rotation, are common; but attacks of vertigo are encountered occasionally. Dizziness on stooping, or on rising suddenly to the erect posture, seems to be commoner in

rity; the patient may hold on to a support for several seconds or a minute, and the attack passes. In other instances attacks may be so frequent that the patient is afraid to leave home or to cross the street. Such feelings of insecurity are most disturbing to patients, and an account of the symptom may give the impression of a psychoneurotic

The origin of the symptom is of interest. Its lack of association with organic nervous phenomena suggests as a speculative hypothesis that the dizziness is due to a vascular disturbance in the labyrinth.

**Tinnitus**

Tinnitus is not a common symptom in high blood pressure. In some hypertensive patients tinnitus occurs in the absence of any known middle ear disorder and is relieved by blood pressure reduction with methonium compounds Two patients encountered by Dr. Hanna in

due

level

wnt ... as sea-shell noises.

**Tenseness and Aggressiveness**

Certain personality traits ... not universally, among hyp... themselves as "tense", "on ... reason that they knew of, more commonly when there is an unexpected caller at the house, or the telephone rings, or they have a social occasion, or a visit to the doctor. An element of aggression is often present Occasionally aggressive behaviour is overt, but commonly, although the patient is well aware of angry impulses, these may be well concealed in their contacts outside the home

... confidence has been established, many patients who are questioned tactfully, but directly, about this admit that they are hot-tempered, and a trouble to their family and not

infrequently will break down and weep. Sometimes patients have less insight into their aggression.

Much of the emotional unrest in these patients is only revealed on direct enquiry; and usually they welcome and benefit from a discussion. Some hyperdynamic individuals apparently have found an outlet for the expression of latent aggression in their active pursuit of business, profession or sport.

The subject is considered in more detail in Chapter VII.

## Various Haemorrhagic Manifestations

Recurrent haemorrhages from one site or another may be complained of by hypertensive patients. Examples are: epistaxis, menorrhagia, metrorrhagia, haematemesis, haemoptysis and subconjunctival haemorrhages. Unexplained bouts of visceral pain might, in some instances, be due to small tissue haemorrhages. Cerebral, retinal, and labyrinthine haemorrhages are referred to elsewhere. No doubt the *relative importance of local lesions and elevated blood pressure* in promoting recurrent haemorrhages varies from patient to patient.

*Epistaxis.* — The relationship to high blood pressure is well known. Some patients seem susceptible and have recurrent bleeds, others do not exhibit the symptom.

*Menorrhagia and metrorrhagia.* — Excessive menstrual bleeding is not uncommon and its relationship to hypertension is substantiated by the improvement which occurs when the blood presure is reduced. Intermenstrual bleeding also occurs. The relationship between excessive menstrual and intermenstrual bleeding and hypertension should not obscure the fact that a local pathological state is often responsible, even when bleeding is stopped by procedures which reduce the blood pressure. This applies particularly to intermenstrual bleeding and has occurred in our experience in association with uterine fibroids.

*Haemoptysis* may occur as the result of pulmonary congestion and without evidence of any other exciting cause. In some instances there may be small patches of pneumonitis and the relationship to the hypertension is doubtful.

*Haematemesis* for which no explanation is found is attributed sometimes to hypertension. A hypertensive patient, who had several unexplained haematemeses within a few months, was treated by methonium salts in the hope of preventing a recurrence. She has been on treatment over four years without further haematemesis. It may be that these occurrences were coincidental.

*Renal epistaxis.* — The term is used to distinguish between continued *microscopic* haematuria and a fairly gross bleed into the urinary tract.

*Haemospermia* is referred to by Fishberg (1954) as a condition which is not excessively rare. It occurs without important sequelae.

## COMMENT ON THE EXTENT TO WHICH CERTAIN HYPERTENSIVE SYMPTOMS ARE PSYCHOGENIC

As symptoms are experienced, and knowledge of them is conveyed to the doctor through activity of the patient's mind, it follows that all symptoms must be to some extent an expression of the patient's personality. Riseman and Weiss (1930) went further. They felt that there was no characteristic symptomatology of arterial hypertension and that the symptoms complained of were psychogenic. They made this statement because they found that normotensives at the menopause or with obesity or psychoneurosis, showed symptoms which they also encountered in their cases of arterial hypertension This statement may be misunderstood unless it is realized that they referred to uncomplicated hypertension, which they defined as persistently elevated arterial blood pressure without *evidence of impaired cerebral*, cardiac or kidney function They made a study of symptoms which had an incidence of more than 10 per cent in groups of patients with chronic constipation, obesity, chronic hypertrophic arthritis, psychoneurosis, menopause with normal blood pressure and menopause with *hypertension*. Symptoms such as headache, dizziness, aches and pains, dyspnoea, nervousness, nycturia, tinnitus, weakness and palpitation, occurred in most of the disorders Evidently, such symptoms may occur coincidentally in patients with hypertension and cannot be accepted as due in all cases to the hypertension Ayman (1930) and Stewart (1953) also consider that many of the symptoms, particularly headache, are psychoneurotic.

Evidence that headache, dizziness, breathlessness and sometimes palpitation, in severe hypertension are usually related to the disorder, is the fact that these symptoms commonly disappear during effective treatment, and in our experience seldom recur during periods of observations extending now over six years. In patients who are inherently neurotic, we have found no drug treatment which consistently, and for long periods, gives relief.

These arguments for a specific relationship between hyperten- and the common [illegible]
forms of treatm[illegible]
views with the [illegible] [illegible]logical value, and some of the relief from symptoms must be attributed to this.

## THE MALIGNANT PHASE OF HYPERTENSION

The term "malignant" hypertension is almost as difficult to define as to discard. Its use implies a severe [illegible]

[illegible] has been used to describe [illegible] clinical disorders, a group of pathological changes and a

condition induced experimentally in animals. Although patients exhibiting the clinical manifestations often exhibit also the pathological changes, this does not happen invariably. Also, patients who exhibit the typical pathological changes at autopsy have not necessarily exhibited clinically recognizable malignant hypertension in life.

## Pathology

The most characteristic lesion of malignant hypertension was first



Fig V 6a

The section is of renal tissue from a case of malignant hypertension The arrows point to regions of necrosis in the walls of small arterial vessels

shown by Fahr (1919) to be arteriolonecrosis. Necrotic changes in the walls of small arteries and arterioles cause loss of their normal structure and staining properties (Fig. V 6a). Part or all of the wall may be affected. Another change is a concentric collagenous endothelial thickening which has a laminated, onion skin appearance (Fig. V 6b). This change leads to great reduction of the lumen in affected blood vessels. Some

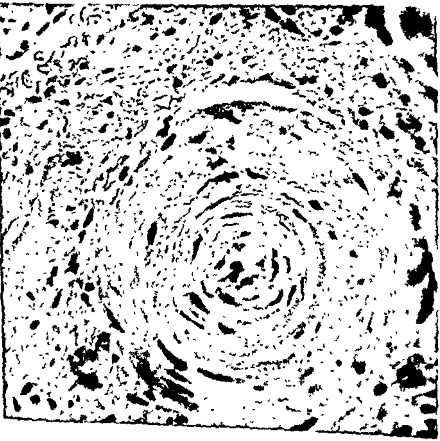


Fig V 6b

The section is from a case of malignant hypertension and shows a small arterial vessel with typical "onion skin" hyperplasia

authorities accept the endothelial changes as indicative of malignant hypertension, in the absence of [illegible]
when present, is most likely [illegible]
and in their interlobular a[illegible]
pancreas, adrenals and intestines are often affected and according to Koepsell et al (1950) the vessels of skeletal muscle are frequently affected Thickening of the walls of small arterial vessels is often seen

in malignant hypertension (Fig. 6c), but also in less advanced hypertensive states.

The clinical and pathological features of "malignant hypertension" may be found in association with almost all types of severe hypertension [18, 19, 34], and usually represent a late or terminal phase of the illness. Thus, the pathological as well as the clinical criteria of malignant hypertension have been described as developing in the course of essential hypertension, pyelonephritis, chronic glomerulonephritis, polycystic kidney, post-pregnancy toxaemia hypertension, polyarteritis nodosa, phaeochromocytoma, Cushing's syndrome, and a variety of disorders usually involving curtailment of the circulation through one or both kidneys (Chapter VI). Hence, it is becoming

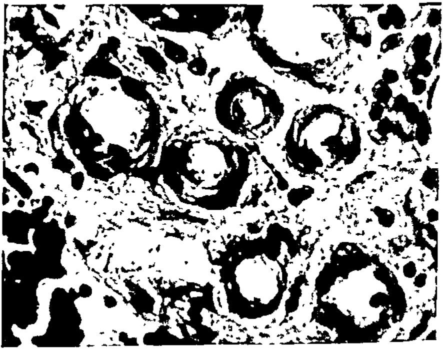


Fig V 6c
The section shows hypertrophy in the walls of arterioles

customary to speak of the malignant hypertensive phase of essential hypertension or of chronic pyelonephritic hypertension When the term malignant hypertension is used by itself it usually refers to the malignant phase of essential hypertension Herxheimer (1924) raised the question of whether the pathological changes in arteriolonecrosis and arteriolosclerosis represented different grades of severity of the same disorder or whether some additional factor was responsible for the occurrence of arteriolonecrosis. The suggestion that both changes result from exposure of blood vessels to hypertension (Ellis, 1938,

Byrom and Wilson, 1939; and Pickering, 1952) has much to commend it. Either arteriolosclerosis alone or in combination with arteriolonecrosis may arise in the various types of hypertensive disease irrespective of the primary cause. Furthermore, in experimental animals, procedures which elevate the blood pressure may lead either to arteriolosclerosis or to arteriolonecrosis if the hypertension is sufficiently severe. Strong evidence in the same direction comes from the many ex- [illegible] IX) and clinical experiences (see Chapter [illegible]

[illegible] not exhibit severe histological changes, and [illegible] struction of the renal artery protects the kidney against the effects of high blood pressure.

In accepting the view that an excessively high blood pressure, or [illegible]

[illegible] by damage of the arteriolar wall make it less well able to tolerate the effects of high pressure or excessive vasoconstriction. In this connection the observations of Klemperer and Otani (1931) are of interest. At the edge of aseptic renal infarcts they found glomeruli resembling those of malignant hypertension in every respect.

### Clinical Criteria of Malignant Hypertension

Probably there are no clinical criteria which make it possible to state during the patient's lifetime that the characteristic lesions of malignant hypertension will be seen in arterioles and small arteries at autopsy. Indeed, renal biopsies indicate that certain patients [illegible]

in the biopsy samples [illegible] we have adopted the practice of [illegible] diagnosing malignant hypertension clinically unless [illegible] present [illegible]

We e[illegible]

severe [illegible] manifestations, and if this is lacking, doubts may be raised about the diagnosis, as in a recent case which proved to be a meningioma. The presence or absence of papilloedema as a means of separating a group of particularly severe cases has the advantage that it provides a classification which is useful, widely used and easily understood; it allows the findings of various clinics to be compared with the Keith-Wagener collection of cases and with other clinical collections which have been classified in this way. In adopting this practice we recognize that some patients with grade 3 changes in the retinal fundi may prove at autopsy to be examples

J

of malignant hypertension as judged by the presence of arteriolonecrosis and concentric endothelial hyperplasia. Thus in a series of 68 patients with the diagnosis of malignant hypertension established at autopsy, Goldring and Chasis (1944) found that papilloedema was absent in 23 per cent. For most clinicians the presence or absence of papilloedema is their main clinical criterion of the presence or absence of a malignant phase of hypertension [22, 27, 34, 48, 63, 65, 78]. It is of interest in this connection that Keith and Wagener (1951) have observed the spontaneous recession of papilloedema in 15 cases. Other less characteristic indications: a high level of the diastolic pressure, albuminuria, microscopical haematuria and a tendency to develop renal insufficiency, are usually referred to as influencing the diagnosis [30, 44, 48].

Koepsell et al. (1950) and Schroeder (1953) are prepared to accept certain grade 3 cases as examples of malignant hypertension. Short of papilloedema with definite elevation of the optic disc, there are many cases with severe hypertension in which retinal oedema occurs in the region of the optic disc, which may creep on to the edge of the disc, blurring its outline. It is probable that many of these cases, though placed in the Keith-Wagener grade 3, have a very similar significance to frank papilloedema. Although the classification on the basis of papilloedema is most useful its arbitrary nature is indicated by the fact that, in many early cases, one disc shows definite papilloedema when the other does not. The eye grading, therefore, although made the basis of a classification, is no more than a local clinical manifestation and sign revealing the seriousness of the clinical state and indicating the probability that certain characteristic pathological lesions of small arterial vessels are already present or may be discoverable at some subsequent date in the absence of treatment The papilloedema may be associated with considerable visual impairment.

Usually papilloedema is associated with the presence of hard and soft retinal exudates and haemorrhages, but this is not invariably the case. Changes in the arterioles at the arteriovenous crossings or local narrowing of arteries are frequently encountered, but in some instances where the hypertension is acute, arterial changes may be minimal. As Shelburn et al. (1932) showed, the presence of papilloedema is often accompanied by a rise of the cerebro-spinal fluid to above 200 mm. of water. This observation has been confirmed by Pickering (1934). The development of papilloedema and other advanced retinal changes are closely related to the height of the blood pressure but it is possible that the relationship is not always a direct one. Perera (1954) described 6 patients, formerly hypertensive, whose blood pressures fell to near normotensive levels following a myocardial infarction in 3 cases, a cerebral thrombosis in 1 case and sympathectomy in 2 cases. Nevertheless, during the normotensive period papilloedema developed, which in some cases at least was bilateral. A possible

though speculative explanation is that vasospasm affecting the retinal vessels, though unassociated with generalized blood pressure increase, led to papilloedema by causing local vascular damage. Certainly, exudative retinal changes including papilloedema are dispersed regularly by adequate blood pressure reduction using methonium salts (Smirk and Alstad, 1951).

Clinically there appears to be no sharp line of distinction between advanced, severe cases of essential hypertension and cases of malignant hypertension, unless the presence or absence of papilloedema is used as the criterion for their separation. If we compare cases of essential hypertension in the malignant phase and cases of essential hypertension not exhibiting the malignant phase, there are certain distinctions apart from papilloedema which are likely to be encountered. The cases in the malignant phase are much more likely to exhibit evidence of renal damage. When first seen a proportion of these cases show a decrease in the renal concentrating capacity and nitrogen retention but many cases have normal or nearly normal renal excretory functions [14, 71]. There may be albumin in the urine, however, and the urine deposit may contain red cells and casts. Exceptionally the urine is normal. In a group of 100 cases of malignant hypertension Piette and Corcoran (1954) found the mean protein excretion was 2.3 gms. per 24 hours, and the range 0.0 to 21 gms. They consider that the albuminuria is due at least in part to the high blood pressure. The disappearance of albuminuria in many cases, on treatment with ganglion blocking agents is consistent with this view. Even when the renal function is satisfactory the subsequent course of patients with malignant hypertension indicates that they are much more liable to develop substantial renal damage than are the non-malignant cases of essential hypertension (Ellis, 1938). Severe renal damage may occur within a few months and uraemia is an important cause of death.

The clinical picture may be much modified by treatment; indeed in our own series of cases treated by ganglion blocking agents there has been little evidence of the occurrence of severe renal damage in patients who exhibited no substantial defect at the time treatment started

Pallor is much more frequently present in malignant hypertension than in benign essential hypertension. The difference is due sometimes to anaemia, and sometimes to constriction of the small blood vessels of the skin Volhard and Fahr (1914) were so impressed by this difference that they referred to malignant hypertension as pale hypertension and to essential hypertension as red hypertension. Volhard (1948) adhered to this classification to the time of his death. The use at the present time of a somewhat diff-

directed attention to the clinical and pathological features distinguishing the benign from the malignant forms of hypertension.

In malignant hypertension, there is an added liability to such cerebral manifestations as severe headaches and encephalopathy, and in cases where the renal function is defective, to epileptiform convulsions. The risk of cerebral haemorrhage is greatly enhanced, as is also the risk of cardiac decompensation. These manifestations, and most others, are of a kind which are encountered also in severe cases of essential hypertension without papilloedema but they occur earlier in malignant hypertension. In the lungs, congestive changes secondary to heart failure or cardiac asthma may occur and, in addition, pulmonary oedema is not infrequent, particularly when there is much nitrogen retention.

Arteriolonecrosis has been demonstrated in intestinal blood vessels and intestinal ulcers may form which, on occasion, may bleed (Cunningham, 1948). Abdominal pain is also cited by some authors (Goldring and Chasis, 1944) as occurring rather frequently in cases of malignant hypertension.

## COMPLICATIONS OF HYPERTENSION

The justification for a separate heading "complications of hypertension" is that, whereas the conditions described as "clinical manifestations of hypertension" are for the most part reversible when the blood pressure is reduced, the various clinical conditions to be described are complications, in the sense that they represent disorders related to essential hypertension, but, once they have developed, there is no expectation of reversing the disorder by blood pressure reduction. For this reason, though the decision was a difficult one, encephalopathic attacks and angina have been classified under clinical manifestations, whereas cerebral thrombosis, cerebral haemorrhages and cardiac infarction have been classified under complications. Often, there is no sharp distinction between a clinical manifestation and a complication, and malignant hypertension lies between the two, but is more a manifestation than a complication if reversibility is to be the criterion

### Brain Pathology in Hypertension

The cerebral blood vessels of hypertensive patients usually exhibit hypertrophy of the media and the internal elastic lamina is reduplicated. Lichtenstein (1949) also points out that there will usually be thickening of the subintimal tissues.

Cerebral arteriosclerosis is accelerated by hypertension. This may lead to shrinking of the brain substance and sometimes to multiple small areas of cerebral softening. The symptoms may be comparatively inconspicuous. Even at autopsy it is not always clear whether areas of

softening have been due to arteriosclerotic processes only, or whether additionally there has been thrombotic occlusion.

It is generally agreed that hypertensives, as compared with normotensives, will have a higher proportion of cerebral haemorrhages. In normotensives cerebral thrombosis is much more frequent than haemorrhage.

Dr. Dorothy Russell (1954) found that 232 out of her autopsy series of 461 patients with cerebral haemorrhage were hypertensive. The location of haemorrhage in these patients was into: the basal ganglia

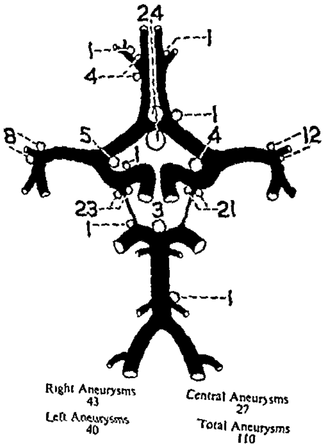



*Fig* V 7

Sites of aneurysms demonstrated angiographically in 100 patients (Falconer, M. A., Proc. roy. Soc. Med, 47 : 693, 1954).

in 151, the cerebral white matter in 21, the pons and mid-brain in 32, the cerebellum in 18, the subcortical region in 4, and into the meninges in 6 cases In malignant hypertension and in nephritis a higher proportion of the haemorrhages took place into the brain stem.

In some patients with hypertension the haemorrhage is subarachnoid, the usual explanation being the rupture of a berry aneurysm. Leakage or rupture is somewhat more likely to occur in hypertension than in normotension. It is generally believed now that the berry aneurysm is due to an enlargement in later life at the site of a congenital defect in the media of a cerebral artery. The aneurysms are nearly always found at arterial bifurcations. Some haemorrhages occur at the site of arteriovenous malformations (Fig. V 7). It has been pointed out by Falconer (1954) that the cerebral aneurysms leak but rarely rupture, the quantity of blood entering the subarachnoid space being a matter of a few ml.

## Cerebral Haemorrhage

Cerebral haemorrhage, one of the most important complications of high blood pressure, may be massive and cause death within a day or two, being associated with profound unconsciousness and the presence of blood in the cerebro-spinal fluid; but sometimes the haemorrhage may be small and circumscribed, even in hypertension. One patient in our series, complaining only of headache and diplopia, was shown to have blood in the cerebro-spinal fluid. The difficulties which may occur sometimes in distinguishing such attacks from encephalopathy have been referred to already in this chapter.

Haemorrhage into the brain substance is often from the lenticulostriate artery, the so-called "artery of cerebral haemorrhage" but other sites are common. Spontaneous haemorrhage into the brain substance may sometimes be due to simple rupture of an artery, when symptoms have a sudden onset without previous warning and the patient becomes rapidly unconscious. Haemorrhages sometimes occur when, as the result of thrombosis or of ischaemia, there has been focal softening of the brain; the lack of external support or, more probably, damage to the vessel wall predisposing to haemorrhage. In such instances there may be prodromal nervous manifestations. In some instances the haemorrhage is not massive but petechial

## Cerebral Softening from Thromboses and other Causes

The incidence of cerebral thrombosis is not increased as much by hypertension as is the incidence of cerebral haemorrhage In most instances thrombosis probably depends upon the occlusion of an atherosclerotic cerebral vessel. Usually it is not possible, either clinically or at autopsy, to distinguish between brain softening due to narrowing of vessels by atheroma alone and softening due to closure of an atheromatous vessel by a clot. It is also difficult, clinically, to determine the extent of the brain damage, in the sense that a fairly large area of softening in one of the "silent" areas of the brain may induce fewer clinical manifestations than a smaller one in the internal

capsule. Some of the lesions which are described as minor thromboses may only be minor in the sense that there has been little motor and sensory involvement. The disabilities induced by a "minor" cerebral thrombosis may improve rapidly in the course of a few days or weeks, leaving few residual symptoms. The clinical distinction between the "minor" cerebral thromboses and substantial encephalopathic attacks is usually conjectural and may also remain doubtful at an autopsy. An encephalopathic attack becomes a more likely diagnosis when there is clinical evidence of an extensive lesion from which there is rapid recovery, perhaps within an hour or so. In minor thromboses the changes in central nervous function are usually less widespread and take longer to clear and often leave some residue. Logically there is no reason why a substantial vascular spasm which we may describe as encephalopathy should not give rise to cerebral softening.

This would be more likely to occur in a region where the blood supply was already restricted as the result of organic vascular changes. Cerebral thromboses are usually gradual in their spread and are often preceded by such prodromal manifestations as transient limb pareses, aphasia, tingling or other subjective sensations.

Cerebral thromboses have been described as occurring following considerable decrease in the blood pressure in patients with hypertension. Our experience has been that lowering of the blood pressure, by ganglionic blockade, has greatly decreased the incidence of cerebral vascular accidents. It is possible that excessive or prolonged hypotension induced in this way might cause thrombosis. In our series of hypertensive patients under treatment, cerebral vascular accidents usually started at a time when the blood pressure was at a high level.

Thrombosis of a carotid artery may be responsible for a hemiplegia [31] and may occur in *hypertension*. Sometimes, however, there are no nervous manifestations at the time of a carotid artery thrombosis, but these may occur later in a series of embolic episodes, due to the dislodgement of clots.

While we remain uncertain of the utility of lowering the blood pressure at the time of a cerebral haemorrhage we are inclined to think that this is desirable. In cerebral thrombosis we had a number of discouraging experiences. When the blood pressure was lowered, there appeared to be an increase in the extent of the disability which, however, recovered quickly when the blood pressure [illegible]
lowering the [illegible]
by hyp[illegible]
pressur[illegible] [illegible] to postpone the development of such changes.

## Labyrinthine Haemorrhage

Haemorrhage may take place into the labyrinth and may give rise

In some patients with hypertension the haemorrhage is subarachnoid, the usual explanation being the rupture of a berry aneurysm. Leakage or rupture is somewhat more likely to occur in hypertension than in normotension. It is generally believed now that the berry aneurysm is due to an enlargement in later life at the site of a congenital defect in the media of a cerebral artery. The aneurysms are nearly always found at arterial bifurcations. Some haemorrhages occur at the site of arteriovenous malformations (Fig. V 7). It has been pointed out by Falconer (1954) that the cerebral aneurysms leak but rarely rupture, the quantity of blood entering the subarachnoid space being a matter of a few ml.

### Cerebral Haemorrhage

Cerebral haemorrhage, one of the most important complications of high blood pressure, may be massive and cause death within a day or two, being associated with profound unconsciousness and the presence of blood in the cerebro-spinal fluid; but sometimes the haemorrhage may be small and circumscribed, even in hypertension. One patient in our series, complaining only of headache and diplopia, was shown to have blood in the cerebro-spinal fluid. The difficulties which may occur sometimes in distinguishing such attacks from encephalopathy have been referred to already in this chapter.

Haemorrhage into the brain substance is often from the lenticulostriate artery, the so-called "artery of cerebral haemorrhage" but other sites are common. Spontaneous haemorrhage into the brain substance may sometimes be due to simple rupture of an artery, when symptoms have a sudden onset without previous warning and the patient becomes rapidly unconscious. Haemorrhages sometimes occur when, as the result of thrombosis or of ischaemia, there has been focal softening of the brain; the lack of external support or, more probably, damage to the vessel wall predisposing to haemorrhage. In such instances there may be prodromal nervous manifestations. In some instances the haemorrhage is not massive but petechial.

### Cerebral Softening from Thromboses and other Causes

The incidence of cerebral thrombosis is not increased as much by hypertension as is the incidence of cerebral haemorrhage. In most instances thrombosis probably depends upon the occlusion of an atherosclerotic cerebral vessel. Usually it is not possible, either clinically or at autopsy, to distinguish between brain softening due to narrowing of vessels by atheroma alone and softening due to closure of an atheromatous vessel by a clot It is also difficult, clinically, to determine the extent of the brain damage, in the sense that a fairly large area of softening in one of the "silent" areas of the brain may induce fewer clinical manifestations than a smaller one in the internal

hypertension. Harrison and Wood also point out that atherosclerosis does not necessarily cause coronary narrowing. It is their belief that in hypertensive patients the coronary arteries are usually large and with smooth bores, and they consider that the size of the coronary arteries varies directly with the heart weight in hypertrophied hearts. Stewart, Birchwood and Wells (1935) also consider that atheroma does not necessarily lead to ischaemia.

Davis and Klainer (1940b) found that, in patients with angina [illegible]

[illegible]

of the hypertrophied muscle. This may occur even when coronary atherosclerosis is not marked.

Elevation of the blood pressure in females is evidently an important predisposition towards coronary disease. In the male the position is less well defined. One suggestion which has been made is that coronary disease and hypertension are due to a common cause but not directly interrelated. There is, however, good evidence that, in patients with coronary disease, the symptom of angina is more likely to arise when the work of the heart is increased by blood pressure elevation.

With the advent of hypotensive therapy much thought has been given to the possibility that lowering of the blood pressure might lead to cardiac infarction. This topic is considered in Chapter XIX [illegible] it may be stated here that e[illegible] may lead to cardiac infarc[illegible] blood pressure to near normal levels usually decrease anginal pain, and do not appear to increase the incidence of cardiac infarction.

### Branch Bundle Block

The occurrence of branch bundle block in hypertensive patients is usually thought to be due to coronary arteriosclerosis, although this may be localized and may be unaccompanied by other evidence of ischaemia. In some instances branch bundle block is the result of cardiac infarction. Usually the branch bundle block pattern is permanent but occasionally there is a temporary return to a more normal picture. The association with hypertension is due, presumably, to the more frequent occurrence of coronary arteriosclerosis in hypertensive patients. The prognosis of branch bundle block depends upon the underlying cause and varies considerably.

### Dissecting Aneurysm

Dissecting aneurysm is due either to a cystic degeneration of the media or to arteriosclerosis and the dissection nearly always involves the aorta primarily. It is due to deep penetration of the

to attack of Ménière's disease with acute vertigo and vomiting. In general the condition subsides gradually.

## Major Retinal Haemorrhages

Occasionally considerable haemorrhages take place into the eye in patients with high blood pressure. This may involve a considerable amount of the retina and lead to detachment, or the haemorrhage may take place into the vitreous. Almost complete loss of useful sight may occur and may persist indefinitely, though we have encountered patients whose sight recovered over a period of several months and eventually became almost normal. In some patients haemorrhages recur in the same eye, the opposite eye being almost unaffected. Such haemorrhages are an important indication for treatment, to save the affected eye and in hope of preventing haemorrhage in the healthy eye.

## Cardiac Infarction

The question of whether the incidence of cardiac infarction is higher in hypertension than in normotension has been the subject of several clinical studies.

Davis and Klainer (1940a) state that in patients under fifty with hypertension there is a high incidence of coronary disease, but they found no relationship between the degree of coronary disease and the degree of hypertension. The association of coronary arteriosclerosis with hypertension occurred in both sexes.

The relationship between "hypertension" and cardiac infarction, however, may depend to some extent upon the level of the blood pressure which is accepted as high enough to be called hypertensive. In a statistical analysis by Master (1953) it was pointed out that if blood pressures over 150 systolic, 90 diastolic are accepted as hypertensive then 56.5 per cent of men and 80 per cent of women were hypertensive prior to their cardiac infarction. If, however, Master's own scale of "normal" is employed (see Chapter III) the frequency of hypertension before the attack averaged 27.2 per cent in men and 71 per cent in women. Master, therefore, considers that hypertension does not predispose to coronary disease in men but is a definite and important predisposition in women.

Harrison and Wood (1949) made a clinical and pathological study of hypertensive and ischaemic heart disease. They conclude that hypertension probably does predispose to coronary sclerosis but they think the relationship has been overstressed. They point out that considerable myocardial hypertrophy may occur as the result of coronary sclerosis in the absence of hypertension and they speak against the common assumption by pathologists that, in the absence of other recognizable causes, hypertrophy of the heart to over 500 g. indicates

[illegible] the concept of cardiac failure in the light
4 [illegible] n Med., 37: 849, 1952.
[illegible] ant hypertension with
5 [illegible] report of a case Brit. med. J., 1: 1070, 1948.

16 Davis, D., and Klainer, M. J. Studies in hypertensive heart disease. I. The incidence of coronary atherosclerosis in cases of essential hypertension. Amer. Heart J., 19: 185, 1940a.

17 Davis, D., and Klainer, M. J. Studies in hypertensive heart disease, III Factors in the production of angina pectoris. Amer. Heart J., 19: 198, 1940b

18 Derow, H. A., and Altschule, M. D. Malignant hypertension. New Engl. J. Med., 213: 951, 1935

19 Derow, H. A., and Altschule, M. D. The nature of malignant hypertension. Ann. intern. Med., 14: 1768, 1941

20 Dexter, L. Pathologic physiology of mitral stenosis and its surgical implication. Bull. N. Y. Acad. Med., 28: 90, 1952.

21 Doyle, A. E. Electrocardiographic changes in hypertension treated by methonium compounds. Amer. Heart J., 45: 363, 1953.

22 Doyle, A. E. Retinal changes in hypertension. Trans. Ophthal. Soc. N. Z., Suppl. N. Z. med. J., p. 39, 1954.

23 Doyle, A. E., and Kilpatrick, J. A. Methonium compounds in the angina of hypertension. Lancet, 1: 905, 1954.

24 Ellis, A. Malignant hypertension. Lancet, 1: 977, 1938

25 Evans, L. R., and White, P. D. Massive hypertrophy of the heart with special reference to Bernheim's syndrome. Amer. J. med. Sci., 216: 485, 1948

26 Fahr, T. Über Nephrosklerose. Virchows Arch. path. Anat., 226: 119, 1919.

27 Fishberg, A. M. Hypertension and nephritis. Lea and Febiger, Philadelphia, 1954

28 Falconer, M. A. The pathology of spontaneous intracranial haemorrhage — Surgical pathology of spontaneous intracranial haemorrhage due to aneurysms and arteriovenous malformations. Proc. roy. Soc. Med., 47: 693, 1954

29 Goldberger, E. An interpretation of axis deviation and ventricular hypertrophy. Amer. Heart J., 28: 621, 1944.

30 Goldring, W., and Chasis, H. Hypertension and hypertensive disease. Oxford University Press, New York, 1944

31 Guirdjian, E. S., and Webster, J. E. Stroke resulting from internal carotid artery thrombosis in the neck. J. Amer. med. Ass., 151: 541, 1953

31a Goldstein, F., Jenson, W. K., Waldron, J. M., and Duncan, G. G. The relationship between hypertension and coronary occlusion. Ann. intern. Med., 44: 446, 1956.

32 Halmágyi, D., Felkai [illegible] Z. The role of [illegible] arterial hypert[illegible] 16, 1953

33 Harrison, C. V., and [illegible]ood, P. Hypertensive and ischaemic heart disease. Brit. Heart J., 11: 205, 1949

34 Heptinstall, R. H. Malignant hypertension: A study of fifty-one cases. J. Path. Bact., 65: 423, 1953

35 Heptinstall, R. H. Renal biopsies in hypertension. Brit. Heart J., 16: 133, 1954.

36 Herxheimer, G. Über Arteriolonekrose der Nieren. Virchows Arch. path. Anat., 251: 709, 1924

37 Hope, J. A treatise on the diseases of the heart. Philadelphia, 1842. Cited

cystic or atherosclerotic lesion which allows the blood to split up the medial coat. It occurs in the absence of hypertension but is much more common in hypertensive disease. Usually, but not invariably, the onset is with violently acute pain which may be retrosternal and often involves the back and legs and occasionally the arms. The pain is accompanied by a profound shock. The dissection of the aorta may occlude the vessels which supply the spinal cord causing paralysis or other evidence of a spinal cord lesion. The renal vessels may be dissected and the interference with the renal circulation may cause hematuria, anuria and renal hypertension if the patient survives the initial shock. The femoral pulse may be lost. The dissected aorta often leaks or bursts into a pleural space or into other body cavities. *Ante mortem* diagnoses are now made more frequently. Sometimes when there is much calcification a split in the aorta may be recognized at x-ray examination. In one or two instances we have induced maximal lowering of the blood pressure in order to diminish the risk of rupture. The condition is usually fatal within a few days.

## References


1 Allen, E V., Barker, N W, and Hines, E. A., Jr. Peripheral vascular disease. W B Saunders Company, Philadelphia, 1946.
2 Atlas, D H, Eisenberg, H. L., and Gaberman, P Bernheim's syndrome: Report of a case. Circulation (N Y.), 1: 753, 1950.
3 Ayman, D An evaluation of therapeutic results in essential hypertension. I The interpretation of symptomatic relief J. Amer med. Ass., 95: 246, 1930.
4 Bechgaard, P. Electrocardiographic investigation of 264 cases of hypertension. Brit med. J., 2: 1089, 1949.
5 Bercu, B. A, Rokaw, S. N., and Massie, E Antidiuretic action of the urine in patients in cardiac failure. Circulation (N.Y.), 2: 409, 1950.
6 Bernheim. De l'asystolie veineuse dans l'hypertrophie du coeur gauche par stenose concomitante du ventricule droit. Rev Médecine, 30: 785, 1910.
7 Blumgart, H. L., Schlesinger, M J, and Davis, D Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings. Amer. Heart J., 19: 1, 1940.
8 Brunn, F. Über Asthma cardiale. Zbl inn. Med, 49: 873, 1928
9 Burch, G., Reaser, P., and Cronvich, J Rates of sodium turnover in normal subjects and in patients with congestive heart failure. J. Lab. clin. Med., 32: 1169, 1947.
10 Burwell, C. S, and Smith, W. C. The output of the heart in patients with abnormal blood pressures. J. clin. Invest., 7: 1, 1929.
11 Byrom, F. B. The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension (experimental evidence from the hypertensive rat). Lancet, 2: 201, 1954.
12 Clawson, J. Coronary sclerosis — An analysis of nine hundred twenty-eight cases. Amer. Heart J., 17: 387, 1939
13 Cottrell, J. D., and Cuddie, D. C. The arm-to-tongue circulation time in chronic asthma. Brit.. med J., 1: 70, 1942

14 COURNAND, A. A discussion on the concept of cardiac failure in the light of recent physiologic studies in man. Ann. intern. Med., 37: 649, 1952
15 CUNNINGHAM, G. J. Intestinal lesions in malignant hypertension with report of a case. Brit. med J., 1: 1075, 1948
16 DAVIS, D., and KLAINER, M. J Studies in hypertensive heart disease. I. The incidence of coronary atherosclerosis in cases of essential hypertension Amer Heart J., 19: 185, 1940a.
17 DAVIS, D., and KLAINER, M J Studies in hypertensive heart disease. III. Factors in the production of angina pectoris. Amer. Heart J., 19: 193, 1940b.
18 DEROW, H A., and ALTSCHULE, M. D. Malignant hypertension. New Engl. J Med, 213: 951, 1935
19 DEROW, H. A, and ALTSCHULE, M. D The nature of malignant hypertension Ann intern Med., 14: 1768, 1941.
20 DEXTER, L. Pathologic physiology of mitral stenosis and its surgical implication Bull N Y. Acad Med, 28: 90, 1952.
21 DOYLE, A E Electrocardiographic changes in hypertension treated by methonium compounds Amer. Heart J, 45: 363, 1953.
22 DOYLE, A E. Retinal changes in hypertension. Trans. Ophthal Soc. N. Z, Suppl. N Z med J, p 30, 1954
23 DOYLE, A. E., and KILPATRICK, J A. Methonium compounds in the angina of hypertension Lancet, 1: 905, 1954
24 ELLIS, A Malignant hypertension Lancet, 1: 977, 1938
25 EVANS, L. R., and WHITE, P D Massive hypertrophy of the heart with special reference to Bernheim's syndrome. Amer. J med Sci, 216: 485, 1948
26 FAHR, T Über Nephrosklerose Virchows Arch path. Anat, 226: 119, 1919.
27 FISHBERG, A M. Hypertension and nephritis. Lea and Febiger, Philadelphia, 1954
28 FALCONER, M A. The pathology of spontaneous intracranial haemorrhage — Surgical pathology of spontaneous intracranial haemorrhage due to aneurysms and arteriovenous malformations Proc roy Soc. Med, 47 693, 1954
29 GOLDBERGER, E. An interpretation of axis deviation and ventricular hypertrophy. Amer. Heart J, 28: 621, 1944.
30 GOLDRING, W., and CHASIS, H Hypertension and hypertensive disease. Oxford University Press, New York, 1944
31 GUIRDJIAN, E. S, and WEBSTER, J E Stroke resulting from internal carotid artery thrombosis in the neck J Amer med Ass, 151: 541, 1953
31a GOLDSTEIN, F, JENSON, W. K., WALDRON, J. M, and DUNCAN, G G. The relationship between hypertension and coronary occlusion Ann intern. Med, 44: 446, 1956.
32 HALMÁGYI, D. [illegible]
Z [illegible]
art [illegible]
33 HARRIS [illegible] and ischaemic heart disease
Br[illegible] J., 11: 205, 1949
34 HEPTINSTALL, R H. Malignant hypertension A study of fifty-one cases J Path Bact, 65: 423, 1953
35 HEPTINSTALL, R. H. Renal biopsies in hypertension. Brit. Heart J, 16: 133, 1954
36 HERXHEIMER, G. Über Arteriolonekrose der Nieren. Virchows Arch path. Anat, 251: 709, 1924
37 HOPE, J A treatise on the diseases of the heart. Philadelphia, 1842 Cited

by *Lombardo*, T. W., and *Harrison*, T. R., Circulation (N.Y.), 4: 920, 1951.

38 Keith, N. M., and Wagener, H. P. Recession of neuroretinopathy during the course of malignant hypertension — Its occurrence in fifteen patients who did not receive direct therapy. Arch. intern. Med, 87: 25, 1951.

39 *Keith*, N. M., *Wagener*, H. P., and Barker, N. W. Some different types of essential hypertension: Their course and prognosis Amer. J. med. Sci, 197: 332, 1939.

40 *Kempner*, W. Treatment of hypertensive vascular disease with rice diet Amer. J. Med., 4: 545, 1948.

41 Kilpatrick, J. A. Unpublished observations.

42 *Kleinfeld*, M., and *Redish*, J. The size of the heart during the course of essential hypertension. Circulation (N.Y.), 5: 74, 1952.

43 Klemperer, P., and Otani, S. Malignant nephrosclerosis (Fahr). Arch. Path. (Chicago), 11: 60, 1931.

44 Koepsell, J. E., *Kuzma*, J. F [illegible] vascular disease (acute) [illegible] d pathologic study of thirty- [illegible]

45 Leatham, A. The retinal vess[illegible] 203, 1949.

45a Leishman, R. *Some retinal manifestations in hypertension. Trans. ophthal* Soc. U.K., 72: 683, 1952.

46 Litchtenstein, B. W. A Textbook of Neuropathology W. B Saunders *Company, Philadelphia*, 1949

47 Maclean, A. R., and Allen, E. V. The clinical value of sleeping in the "head-up" position J Amer. med Ass, 116: 2533, 1941.

47a McDonald, C G. *Diseases of arteries and their relationship to the eye.* Trans. ophthal. Soc. Aust., 5: 9, 1945.

48 McMichael, J Lessons from hexamethonium studies in malignant hypertension. Ciba Foundation Symposium, Hypertension and Neurogenic Factors, J. & A. Churchill Ltd., London, 1954

49 Master, A. M Hypertension and coronary occlusion Circulation (N Y.), 8: 170, 1953.

50 Master, A. M. The etiology of cardiac enlargement in coronary occlusion, hypertension, and coronary artery disease. Amer. Heart J., 47. 321, 1954

51 Master, A. M., Garfield, C I, and Walters, M B Normal blood pressure and hypertension. Lea and Febiger, Philadelphia, 1952.

52 Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: Evidence of "forward failure" as the primary cause of edema. J. clin Invest, 25: 389, 1946

53 Miles, B. E. The clinical significance of gallop rhythm in hypertension. Brit. Heart J., 13: 327, 1951.

54 Mokoloff, R., Ross, G, and Leiter, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. J. clin. Invest., 27: 1, 1948.

55 Oppenheimer, B S., and Fishberg, A. M Hypertensive encephalopathy. Arch intern. Med. 41: 264, 1928.

56 *Osler*, W. *The cerebral complications of Raynaud's disease* Amer. J med. Sci., 112· 522, 1896

57 Page, I H., and Taylor, R. D Pyrogens in the treatment of malignant hypertension. Mod. Conc. cardiovas Dis, 18: 51, 1949.

58 Parrish, A E. The bioassay of adrenal corticoids in the urine of patients with congestive heart failure J. clin. Invest, 28: 45, 1949

59 PERERA, G. A. Development of hypertensive manifestations after the disappearance of hypertension. Circulation (N.Y.), 10: 28, 1954

60 PERERA, G A, and BERLINER, R. W. The relation of postural hemodilution to paroxysmal dyspnea. J. clin. Invest., 22: 25, 1943

61 PICKERING, G W The cerebrospinal fluid pressure in arterial hypertension. Clin Sci., 1 397, 1934.

62 [illegible]

63 [illegible] (N Y), 6: 699, 1952

64 PIETTE, Y, and CORCORAN, A. C. Proteinuria and malignant hypertension. Canad med Ass J., 71: 542, 1954

65 PLATT, R Hypertensive retinopathy and its medical treatment. Quart. J. Med, n s 23. 441, 1954.

66 RAY [illegible]

67 RISE [illegible]

68 RUSSEK, H I, and ZOHMAN, B L. The syndrome of Bernheim as a clinical entity Circulation (N Y), 1 759, 1950.

69 RUSSELL, D S The pathology of spontaneous intracranial haemorrhage — Spontaneous intracranial haemorrhage Proc roy. Soc Med, 47: 689, 1954

70 SAHLI Zweites Referat. Verh dtsch Kongr inn Med, 19: 45, 1901.

71 SCHOTTSTAEDT, M F, and SOKOLOW, M The natural history and course of hypertension with papilledema (malignant hypertension) Amer. Heart J, 45 331, 1953

72 SCHROEDER, H A Hypertensive diseases — Causes and control Henry Kimpton, London, 1953

73 SHELBURNE, S A, BLAIN, D, and O'HARE, J P. The spinal fluid in hypertension J clin Invest, 11 489, 1932

74 SMIRK, F H Observations on the causes of oedema in congestive heart failure Clin Sci., 2· 317, 1936

75 SMIRK, F H Results of methonium treatment of hypertensive patients — Based on 250 cases treated for periods up to 3½ years, including 28 with malignant hypertension. Brit med J., 1: 717, 1954.

76 SMIRK, F H, and ALSTAD, K S Treatment of arterial hypertension by penta- and hexa-methonium salts Brit med J., 1: 1217, 1951

77 SMIRK, F H, ALSTAD, K S, KILPATRICK, J. A, and VEALE, A M. O. Unpublished observations

78 SMIRK, F H, DOYLE, A E, MCQUEEN, E G, and HAMILTON, M. Unpublished observations, 1956

79 SMITHWICK, R H Surgical treatment of hypertension — The effect of radical (lumbodorsal) splanchnicectomy on the hypertensive state of one hundred and fifty-six patients followed one to five years Arch. Surg (Chicago), 49 180, 1944

80 SOKOLOW, M, and LYON, T P The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Amer Heart J, 37 161, 1949

81 STEIN, B R, and BARNES, A R Severity and duration of hypertension in relation to amount of cardiac hypertrophy. Amer. J. med Sci, 216 661, 1948.

82 STEWART, I McD Headache and hypertension Lancet: 1: 1261, 1953

83 STEWART, J D, BIRCHWOOD, E, and WELLS, H G The effect of atheros-

clerotic plaques on the diameter of the lumen of coronary arteries. J. Amer. med. Ass, **104**: 730, 1935.

84 VOLHARD, F., and FAHR, T. Die brightsche, Nierenkrankheit, Springer, Berlin, 1914. Cited by Pickering, G. W., Circulation (N.Y.), **6**: 599, 1952.

85 VOLHARD, F. On pathogenesis of red (essential) arterial hypertension and of malignant nephrosclerosis. Stanford med. Bull., **6**: 13, 1948.

86 WÉGRIA, R. Pharmacology of the coronary circulation. Pharmacol. Rev., **3**: 197, 1951.

87 WEISS, S., HAYNES, E. W., and SHORE, R. The relation of arterial pulse pressure to the hemodynamics of arterial hypertension. Amer. Heart J., **11**: 402, 1936.

88 WEISS, S., and ROBB, G. P. Cardiac asthma (paroxysmal dyspnea) and the syndrome of left ventricular failure. J. Amer med Ass., **100**.1841, 1933

89 WILSON, C, and BYROM, F. B Renal changes in malignant hypertension, Lancet, **1**: 136, 1939.

90 WOLFF, H. G. Headache and other head pain. Oxford University Press. New York, 1948.

## CHAPTER VI

# AETIOLOGY

## HYPERTENSION FROM UNILATERAL RENAL DISEASE

The occurrence, especially in young people, of arterial hypertension in conjunction with a variety of renal lesions, makes it likely that the renal lesions have been the cause of the high blood pressure. In cases where unilateral renal disease has been associated with hypertension, there are many instances in which the blood pressure has fallen after removal of the affected kidney. This also is evidence that there is a renal form of hypertension in man; but the proportion of cases in which such desirable results are obtained is less than was at first supposed.

In animals, hypertension of some months' duration induced by unilateral renal ischaemia sometimes persists, partly or completely, even after the ischaemic kidney is removed. Similarly, in man, where unilateral renal disease has been present for several years, the expectation of a permanent fall of blood pressure after nephrectomy is reduced. Later in life, and particularly over the age of 45, the very high incidence of elevated blood pressure, especially the more moderate elevations, makes it difficult to decide whether a blood pressure rise is due to some renal lesion, such as hydronephrosis, or to a coincidental essential hypertension. Temporary falls of blood pressure following unilateral nephrectomy occur frequently in such patients, which is not surprising, as hypertensives often have substantial falls in blood pressure after any major surgical operation, which may last for several weeks, sometimes for months Where the blood pressure falls are of a permanent character, as happens in a minority of cases, the evidence is better but not free from ambiguity in interpretation. Many hypertensive patients show appreciable blood pressure rises of emotional origin on attending clinics and the fact that further rises take place on raising the possibility of an operation can be readily verified by initiating such a discussion. Some of the less dramatic falls of blood pressure after operative procedures may be the result of accepting as a baseline a pressure which was temporarily elevated during the preoperative stage, but this is not the whole story. Although there are difficulties in interpreting some of the data there are many examples of lasting falls of blood pressure from a great height to normal levels, and these appear to provide clear evidence of an association between

many kinds of renal disease and hypertension. It is almost certain that the hypertension associated with many of the renal disorders referred to below are examples of renal hypertension. In some instances, however, even when renal disease seems to provide the obvious explanation, the hypertension will be coincidental. Hence, interest is directed especially to the course of events in young patients who are much less liable to have essential hypertension.

Especial interest attaches also to the cases of unilateral renal disease in which there is evidence of renal artery obstruction. It seems almost certain that some of these are examples in man of the Goldblatt type of hypertension, though it must be admitted that the manner in which renal artery constriction causes hypertension is still unsettled. Some of the examples of parenchymal disease associated with hypertension are likely to be the result of interference with the renal circulation.

### Unilateral Renal Artery Obstruction

*Absence of a main renal artery* was reported by Howard et al. (1954). The kidney was supplied by small anomalous arteries, some of which were partially occluded. The raised blood pressure returned to normal after removal of the affected kidney. Langley and Platt (1947) also reported a case in which the main arterial trunk was lacking and there were four small renal arteries, but there was some chronic pyelonephritis also. A nephrectomy relieved the hypertension. Doumer et al. (1951) described a similar case; there was temporary relief only from nephrectomy.

*Ligation of aberrant renal arteries* which had caused an obstructive hydronephrosis was apparently the cause for hypertension in two cases described by Arnold et al., (1951), and a somewhat similar case was described by Boeminghaus and Gotzen (1952).

*Atherosclerotic plaques* in a renal artery, usually situated close to the aorta, have been held responsible for unilateral and bilateral renal ischaemia and hypertension in cases described by Blackman (1939) who thought the condition was of frequent occurrence. One of the two cases quoted by Thompson and Smithwick (1952) had arteriosclerotic occlusion of the left renal artery close to the aorta and the blood pressure fell after removal of the left kidney and remained normal for a year. Additional cases with partial occlusion of the renal arteries have been reported by others [1, 230, 294].

Yuile (1944) pointed out, however, that atheromatous plaques in the renal arteries may be secondary to the hypertension rather than the cause of it, since they are usually associated with arteriolar lesions in the kidneys. Primary parenchymal disease, by diminishing renal blood flow at the periphery, may also lead to arteriosclerotic narrowing of the artery. Langley and Platt (1947) described a patient, aged 60, with

... showing obliterative intimal sclerosis. There was, however, ... have ... of

nephrectomy was a failure ... tension is the result of narrowing of the ... ommon, are the ones which ... to the classical Goldblatt ...

the hypertension and did not exhibit arteriolosclerosis. Several ... have pointed out, therefore, that confidence in an arteriosclerotic plaque being the primary phenomenon and hypertension secondary to it, is only justifiable when the ischaemic kidney shows much less arteriolosclerosis than the kidney with a normal blood supply. A causal relationship is also more likely in young patients who are unlikely ...

the first successful treatment by homografting both renal arteries. The patient was aged 25 and the hypertension was alleviated.

*Thrombosis of a renal artery* is one of the commoner unilateral renal lesions which may give rise to hypertension in man [11, 27, 33, 136, 197, 226, 259, 304, 360]. Shea et al. (1948) described an organized thrombosis of the left renal artery causing hypertension which was apparently relieved by nephrectomy, and Perera and Haelig (1952) also observed relief by nephrectomy in similar cases.

Cases of special interest have been described by Malisoff and Macht (1951) who encountered occlusion of a renal artery and hypertension as the result of thromboangeitis and by Goodman (1952) who described malignant hypertension from unilateral renal artery occlusion by thrombosis. Bauer and Forbes (1952) also described a patient with left renal artery narrowing from atheromatous plaques, followed by thrombosis of a renal artery branch. This led to malignant nephrosclerosis of the right kidney, but the left kidney did not show these changes, being protected by the arterial obstruction. A similar case was described by Schwartz and Gross (1949).

*Renal embolism* may cause unilateral renal ischaemia leading to hypertension [31, 40, 44, 118, 258, 348]. A reference to successfully treated cases is made by Perera and Haelig (1952). Blahd et al. (1952) described a patient who developed malignant hypertension secondary to embolism of a kidney. Fishberg (1942) described 5 patients with hypertension due to renal embolism, 3 from mitral stenosis and 2 from cardiac infarction. Bourne (1951) described a patient with hypertension following renal embolism and infarction which was due to

infective endocarditis. The organisms were streptococcus viridans and an unidentified fungus.

*Aneurysm of a renal artery* has been associated with hypertension. Thompson and Smithwick (1952) described the case of a man, aged 35, with hypertension associated with a small aneurysm of the right renal artery. This was filled with recent thrombus and did not pulsate. A right nephrectomy was carried out and the blood pressure fell. Much of the right kidney was involved by infarction. According to Thompson and Smithwick there have been 96 cases reported in the literature. The great danger of renal artery aneurysm is of rupture with fatal haemorrhage. Often the renal arteries are unobstructed and there may be no blood pressure elevation. Hypertension was mentioned in 15 out of the 96 reported cases. Ten patients had nephrectomy performed but, as far as could be determined, the case reported by Thompson and Smithwick was the only one, in the series they collected, in which there was an unequivocal cure of hypertension, for at least a year after operation. Thompson and Smithwick think that the association of renal artery aneurysm and hypertension is often fortuitous and, in their own patient, the areas of the affected kidney which contained comparatively normal tubules and glomeruli showed thickening of the arterial walls by medial proliferation and intimal thickening Howard



Fig VI 1
Aneurysm of a renal artery causing severe hypertension in a child aged 4 (Case of Dr Charles Burns of Wellington, New Zealand)

et al. (1940) described an aneurysm of the left renal artery in a child, aged 5, with persistent hypertension which was relieved by nephrectomy. A further case relieved by nephrectomy has been described recently by Pastor et al (1955), and another successful one by Snyder et al. (1955) where there were two right renal arteries each with an aneurysm in a child of 9 months.

Dr. Charles Burns of Wellington, New Zealand, kindly provided me with details of a case of hypertension in a boy aged 4 with considerable

hypertension due to an aneurysm of a small artery (Fig. VI 1). The hypertension was unresponsive to ganglion blocking drugs. Drs. M. Gray and R. C. S. Dick of Christchurch, New Zealand, encountered a patient aged 21 with hypertension from an aneurysm of a renal artery which was also unresponsive to the administration of a ganglion blocking drug (pentolinium).

*A syphilitic aneurysm* of the abdominal aorta led to renal artery co[illegible] hypertension in a negro patient, aged 28[184]. [illegible]

app[illegible] Riggs and Satterthwaite (1941), and in another [illegible] (1951)

[illegible]

[illegible] may be associated with blood pressure elevation, relieved by nephrectomy. It would seem (Hollingsworth, 1934; Slominski-Laws et al , 1956) that the fistula does not always cause hypertension.

*Obstruction of a renal artery by a foreign body* has been described by Latoret (1953) A 32-year old soldier received a thoracic shrapnel wound and developed hypertension. At autopsy the right renal artery was almost completely occluded by a metallic foreign body. The contralateral kidney had the microscopical appearances of malignant nephrosclerosis.

*Rotation of the renal pedicle.* Adams (1955) has described a patient with hypertension brought about by rotation of the renal pedicle due to a carcinoma of the upper pole of the right kidney. The hypertension (260/140) was relieved by nephrectomy and the patient was alive eight years later.

*A hydatid cyst* causing renal artery compression and *malignant* hypertension was described by Davson (1941)

*Ectopic kidneys* have been associated with hypertension. One of the best examples of a relationship between hypertension and unilateral renal [illegible] (1938). A coloured [illegible] years which was [illegible] by the removal of an ectopic kidney. The authors attributed the hypertension to a plug of smooth muscle within the artery but Howard et al. (1954) state that, on re-examination of the original section, the mass of smooth muscle was shown to be an artefact. There was no renal disease present in the kidney. Moore (1948) described relief of hypertension following the removal of an ectopic kidney in a woman aged 19 The relationship, if any, to renal ischaemia is rather presumptive

*A fibrous band* obstructing a renal artery was the cause of hyper-

tension in a case described by Imber and Clymer (1955). The hypertension was relieved, so far for two years, after nephrectomy.

### Involvement of the Renal Parenchyma

*Hydronephrosis.* — Although hypertension may be associated with unilateral hydronephrosis and unilateral nephrectomy may be successful [247] the expectation of success in hydronephrotic cases is less than in cases with unilateral pyelonephritis (Langley and Platt, 1947). A post-traumatic unilateral hydronephrosis with hypertension, in a young soldier, was described by Heintz et al. (1954) together with an account of some other unusual types of renal hypertension.

*Unilateral pyelonephritis.* — The evidence that unilateral pyelonephritis may be associated with hypertension and that such hypertension may be relieved in a substantial proportion of patients by nephrectomy is well documented. An early example of a deliberate nephrectomy undertaken with the object of relieving hypertension is provided by Butler (1937). Before Butler and even before the epoch-making work of Goldblatt, Ask-Upmark (1929) had obtained a hint that unilateral renal disease and malignant hypertension might be associated.

It is difficult to form an estimate of the proportion of well selected cases of unilateral pyelonephritis in which nephrectomy causes a return of the blood pressure to normal or near normal levels, for there is a natural disposition to report successes; and the literature abounds in reports of one or two apparently successful cases, sometimes followed for an insufficient period after the operation. Pickering and Heptinstall (1953) found that 4 out of 7 cases had a substantial reduction in the blood pressure following nephrectomy. In many series the proportion of successes is less than this. Perhaps one in four or one in three patients may be expected to have a successful result. Many other authors [22, 216, 237] have provided examples of the relief of hypertension by nephrectomy in patients with unilateral chronic pyelonephritis. Weiss and Parker (1939) point out that unilateral pyelonephritis may be associated with malignant hypertension and other examples have been reported, but the evidence that only one kidney is diseased is often presumptive. Graber and Shackman (1956) described three patients aged 28, 33 and 34 who were treated successfully by unilateral nephrectomy. They emphasised the need for separate determination of the renal clearances of the two kidneys before undertaking surgical treatment.

In the series of Barker and Walters (1940a) there is included the case history of a child aged seven and of four adults who were successfully treated by unilateral nephrectomy; and other examples of success in children have been published by Griffiths (1950). The occurrence of substantial hypertension in children is so unusual that its presence in

conjunction with unilateral pyelonephritis and subsequent cure by nephrectomy, is very strong evidence of a causal relationship between the two.

Tanquist (1952), while emphasizing the fact that many unsuccessful cases are unreported, collected from the literature an account of 81 cases of unilateral pyelonephritis associated with hypertension, 57 per cent being relieved by nephrectomy. He lays great emphasis on the need for thorough treatment of pyelitis and pyelonephritis in their earlier stages, with the object of avoiding chronic conditions leading to hypertension.

We are in entire agreement with this and ordinarily administer at least three ten-day courses first of a sulphonamide (gantrisin), 5 to 6 gm. daily; next of ammonium mandelate 45 gr. four times daily with the urine reaction adjusted to pH 5.3; followed by a further course of ten days' duration with the sulphonamide. Urinary cultures may be negative at an early stage of treatment, but the full course is given in any case; for otherwise recurrences may take place even after the urine has ceased to show the presence of organisms. During this programme of therapy pyelographic studies are made and, where there is an indication, mechanical defects are corrected and antibiotics such as streptomycin or terramycin are administered.

No doubt some of the failures with nephrectomy are due to the presence of bilateral renal disease, and perhaps some successes are met even when both kidneys are affected, but one of them slightly. Aside from pyelonephritis there may be unilateral renal ischaemia from an atherosclerotic plaque or some other defect of the remaining kidney and, on occasion, rises of blood pressure may follow nephrectomy due to pre-existing ischaemia of the remaining kidney.

*Renal tuberculosis.* — It is generally agreed that renal tuberculosis does not often give rise to hypertension even when the disorder is bilateral. Cases do occur, however, in which blood pressure elevation seems to be due to this cause. Van Goidsenhoven and VandenBrouck (1946) reported two examples of unilateral renal tuberculosis in which great decreases of the blood pressure followed nephrectomy, the blood pressure falls being maintained for two and twelve years respectively. These authors [illegible]

Read (1956) [illegible]

secondary to [illegible] tuberculosis in a male aged 17, which was treated successfully by nephrectomy with relief of [illegible]

[illegible]

[illegible] hypertension in [illegible] and

tubercul[illegible]

[illegible]

[illegible], especially in the [illegible] gross pathological changes in a kidney are unlikely to

induce hypertension unless there is a sufficient amount of ischaemic renal tissue but authentic examples of hypertension from renal tuberculosis are encountered occasionally.

*Radiation Fibrosis.* — Radiation fibrosis associated with blood pressure elevation has been described. Dean and Abels (1944) mention the case of a woman, aged 20, with apparently normal kidneys and normal blood pressure, who received radiation in the left upper quadrant of the abdomen. Seven years later the blood pressure was observed to be *abnormally high. After removal of a sclerosed kidney* the blood pressure became normal and remained so for fourteen months.

*Renal Calculus.* — It is generally agreed that a unilateral renal calculus does not often lead to hypertension and that, in this condition, hypertension is seldom relieved by nephrectomy. Braasch (1942) states that in his series the incidence of hypertension is no greater among patients with renal calculi than in an equal number of miscellaneous patients without renal calculi. Furthermore, he finds that the incidence of hypertension is no greater with bilateral than with unilateral lithiasis. Not infrequently however, pyelonephritis and renal calculus are associated and it may be difficult to decide which of these is responsible for a blood pressure elevation.

*Circumrenal Haemotoma.* — A number of instances have been published of spontaneous or traumatic perirenal haematomata associated with hypertension and Miller and Cordonnier (1949) describe a patient with a large haematogenous cyst, apparently the result of a spontaneous haematoma, which was associated with hypertension. The hypertension was relieved by nephrectomy. Martin (1949) described a case in which a perirenal haematoma developed and the blood pressure rose to 180/100. The cause of the haematoma was not found. Corry (1946) described four patients with temporary hypertension following injuries to a kidney and Howard et al. (1954) described hypertension from renal damage by a bullet, the blood pressure returning to normal within 24 hours after nephrectomy. A further case has been described recently by Engel and Page (1955).

*Renal Tumours* — Renal tumours have led, on occasion, to compression of a renal artery. Howard et al. (1954) described relief of hypertension following left nephrectomy in a patient with a small tumour mass, a ganglioneuroma, which was lying close to the left renal pedicle. Tests for phaeochromocytoma were negative. A Wilms' tumour in a seven year old girl was responsible for compression of a renal artery and hypertension which was relieved by nephrectomy (Koons and Ruch, 1940). A lymphosarcoma was responsible for renal artery constriction and hypertension in a patient described by Blatt and Page (1939). A perirenal lymphangioma was responsible in a case reported by Pulaski (1950).

... a study of the relationship between hyper-

## Comment on Unilateral Renal Disease and Hypertension

It must be accepted that hypertension may be caused by unilateral renal disease and is often the result of renal ischaemia, even in parenchymal disorders. Some at least of the patients with renal artery obstruction evidently have a Goldblatt type of hypertension. This is not to say that a large majority of patients with unilateral renal disease have hypertension which is initiated by a Goldblatt mechanism. It may be so, but at least in older patients essential hypertension occurs so frequently that rises of blood pressure will often be coincidental. Unfortunately the way in which renal ischaemia leads to and maintains hypertension remains obscure.

Even when the presence of unilateral renal disease is established there are difficulties in deciding on the best course of action. If the patient is under 30, so that a coincidental essential hypertension is ... that hypertension is due to the ...

removing the diseased kidney should be considered. In older patients, however, over-average blood pressures are present in a high proportion of the general population and for this reason nephrectomy may not cause any lasting decrease of blood pressure. Langley and Platt (1947) in a review of published cases report thirteen patients with a family history of hypertension with nephrectomy successful in one, whereas there were eight successes among thirteen cases with a negative family history They advise that all hypertension patients under the age of 45 years and all cases with ...

of familial hypertension should be investigated, as there is a substantial chance that the hypertension may be secondary to renal disease, which if unilateral may respond to surgical treatment. If one kidney is shown to be appreciably diminished in size, the expectation of significant unilateral renal disease of that kidney is increased.

Schroeder and Fish (1940) state that in selecting cases for surgical treatment they think that the ...
for more than two years.
tension of long duration ...
Platt (1947) and Pickering and Heptinstall (1953) cite cases in which hypertension, even of five years' duration or more, was relieved by unilateral nephrectomy.

On occasion unilateral nephrectomy will prove to be a harmful procedure. The condition for which the nephrectomy was undertaken may not have been accompanied by hypertension but, where the remaining kidney is already the site of renal ischaemia, nephrectomy may cause hypertension. Freeman and Hartley (1938) referred to a patient whose sole remaining kidney after nephrectomy had been rendered ischaemic by an atheromatous plaque in the renal artery and malignant hypertension followed the removal of a kidney which had been damaged by a crush injury.

## Relationship between Unilateral and Bilateral Renal Disease in Regard to Hypertension

By analogy with observations in experimental animals it is to be expected that hypertension will be more likely to occur and rise to higher levels when both kidneys are ischaemic or damaged, than when only one is affected. Several authors have commented on the relationship between non-nephritic renal disease and hypertension [50, 73, 223, 244, 251, 254, 352]. Some consider there is a definite relationship between renal disease and hypertension [223, 251, 352], others that there is a relationship in particular instances but that in general there is little increase in the amount of hypertension in patients with non-nephritic renal disease as compared with controls [50, 73, 244, 254]. Pearman et al. (1940) state that in 12,000 patients with hypertension all "surgical" lesions of the kidney amount to 1.7 per cent, pyelonephritis being 1 per cent and calculus being 0.4 per cent. In 500 instances each of various disorders the incidence of hypertension was reported as: in pyelonephritis 9 per cent, in nephrolithiasis 7 per cent, in duodenal ulcer 4 per cent, in diseases of the gallbladder 7 per cent and in bronchial asthma 3 per cent. Maher and Wosika (1939) found in a review of 600 private patients with hypertensive vascular disease that there were 101 patients in which hypertension was combined with some urological condition. Among these they mentioned 31 cases with prostatic obstruction and complications in the upper urinary tract, 27 with chronic pyelonephritis and complications, 18 with renal stones and complications and a number of miscellaneous conditions. Braasch and Jacobson (1940a) made a comparison of patients with pyelonephritis and a control group. In the age groups 30—39, 40—49, 50—59, and 60—69 respectively the incidence of hypertension in the control group was 8.4, 16.4, 28.7, and 47.1 per cent whereas in the group of cases of pyelonephritis the respective incidences were 13.3, 24.5, 39.5 and 53.0 per cent. It seems likely that the incidence of hypertension was increased by the presence of pyelonephritis but the difference is not impressive. This accords with our own experience. Many patients with pyelonephritis do not get hypertension and in many patients with

pyelonephritis the blood pressure elevation is due to coincidental essential hypertension. This latter point is often overlooked.

Almost all of the renal conditions referred to as occurring unilaterally may also occur bilaterally. A number of conditions, however, will now be referred to which have been described as occurring bilaterally but which in some instances may involve only one kidney.

## PYELONEPHRITIS

### Clinical Features

Acute pyelonephritis relates to the subject of high blood pressure only in so far as its occurrence may be the precursor of a chronic pyelonephritis The great majority of cases of acute pyelonephritis leave no clinical residue, and scars unaccompanied by evidence of significant renal impairment may be seen at autopsy. It is doubtful whether the incidence of hypertension in later life is much increased in patients who have had a single attack of acute pyelonephritis. This is not to say that there is no relationship, but that the patients who go on to chronic pyelonephritis and hypertension are a small proportion of the whole. Furthermore, hypertension is so *common* that when a hypertensive patient gives a history of pyelonephritis, one should not draw the conclusion that healed pyelonephritis is likely to be the explanation of the hypertension. There is a good chance that it is coincidental, especially *in older patients*.

The lasting relief of hypertension by nephrectomy in some cases of unilateral pyelonephritis provides evidence amounting to proof that, in certain cases, pyelonephritis causes hypertension. Hypertension is more likely to be induced by bilateral than by unilateral pyelonephritis [352] but cases with clearly documented bilateral pyelonephritis may not exhibit high blood pressure [210, 284, 352]. Analysis of our clinical and autopsy records leads us to the same conclusion.

When renal damage is severe, leading ultimately to death from uraemia, it is evident from published cases [210, 231, 352] [illegible]

[illegible] due to chronic pyelonephritis may be unaccompanied by hypertension [129, 198, 210, 231, 352]. In a group of severe cases Weiss and Parker (1939) found hypertension in [illegible] of 38 patients with [illegible]
hypertensio[illegible]
probably a[illegible]

Many hypertensive patients diagnosed as having chronic pyelonephritis are under the age of 40, and in these comparatively young

patients blood pressure elevations are much more likely to be related to the pyelonephritis than in older patients, who may have essential hypertension coincidentally. It has been stated by Braasch and Jacobson (1940b) that the incidence of hypertension in patients with chronic pyelonephritis is approximately twice that which occurs in non-pyelonephritic people of the same age group. Brod (1956) also finds the incidence of hypertension in young chronic pyelonephritis patients is much above that in the general population of a corresponding age group.

The above statements apply for the most part to studies which have been made on patients with diagnoses of chronic pyelonephritis, made either on good clinical evidence or proved at autopsy. It seems very likely that the incidence of hypertension is much less in the more obscure cases of chronic pyelonephritis.

It is not difficult to suspect the possibility of chronic pyelonephritis in patients who manifest one of the following clinical features:

1. A history of acute pyelonephritis
2. Irritation or pain when passing urine, frequency, or the presence of albumin, frank pus, or red cells in the urine
3. A defect in the renal concentrating power, nitrogen retention or frank uraemia
4. Back pain, unexplained anaemia and a tendency to facial puffiness.

When such clinical indications are present, x-ray examination may provide confirmatory evidence by revealing inequality in the size of the kidneys, or distortion of the renal pelves, though these are not always due to pyelonephritis.

Bacteriological examination of the urine will be undertaken and organisms may be found. There is, however, excellent evidence that some cases of healed pyelonephritis give no history of an *acute* pyelonephritis, may be examined on a number of occasions without exhibiting pus or organisms in the urine, may have no significant decrease in the excretory function of the kidneys, yet may be associated with elevation of the blood pressure [231]. As Rosenheim (1954) has pointed out, the ante mortem diagnosis of healed pyelonephritis is extremely difficult, if not impossible, in such cases.

It is also difficult to decide how many patients who present themselves with elevated blood pressure apparently due to essential hypertension, are in fact examples of pyelonephritis. I find it difficult to believe that such cases occur frequently.

Bechgaard (1946), in a follow-up study of 1000 hypertensive patients, found definite pyelonephritis in 24 patients, 19 women and 5 men. The average age at the first examination was 51 years for the living

and 58 years for the dead. In addition, there were 26 cases in which the diagnosis of pyelonephritis was uncertain. He states that the combination of *nephrosclerosis* and cystitis, which is often encountered in older women, is in practice almost impossible to distinguish in life from ... Hence he says this group must contain, as ... ong to the group of ... with the experience of our clinic. If, however, there is a defect in the renal concentrating power, with or without nitrogen retention, or if the presence of organisms or pus in the urine indicates continued infection, or if there is distortion of the renal pelvis at pyelography, or appreciable inequality in the size of the kidneys, then it is much more likely that ...

... chronic pyelonephritis the two conditions are likely to be related causally. In older people it is tempting to assume a causal relationship, but there may be none.

If it is difficult to define the relationship of hypertension to pyelonephritis when the diagnosis of pyelonephritis is established, it is much more difficult if we start out with a large number of hypertensive patients who give no well-defined history of pyelonephritis, and we seek to determine whether among these patients there are hidden examples of pyelonephritis. Our experience with autopsy evidence has been that, in ... has been some ... evidence upon ... to base a definite diagnosis.

Reports upon the causes of death in pyelonephritis patients vary greatly. In the series of Mansfield et al. (1943) 7 out of the 11 of *healed pyelonephritis* cases died from uraemia and 4 out of 6 of the cases with chronic pyelonephritis still exhibited some evidence of infection. In addition, uraemia was associated with ...

phrit ... excep ...

In contrast, in 1000 postmortem examinations at the Boston City *Hospital*, Kinney and Mallory (1943) found healed pyelonephritis in nearly 14 per cent of all persons. The lesions were sometimes of minor degree and in life the patients often had few or no clinical manifestations referable to their kidneys. They found, however, that the number of such patients who eventually developed renal failure or significant hypertension exceeded the number with sub-acute or chronic glomerulonephritis. In this they agreed with Weiss and Parker (1939).

## Pathogenesis

There is evidence that pyelonephritis may arise by an ascending infection or by infection from the blood stream. A short urethra should facilitate direct invasion of the urinary tract by organisms and the frequency with which pyelonephritis affects children and females is favourable to the view that many infections ascend; but bacteraemia is important also. Bacteraemia occurs after operations on the lower urinary tract and sometimes after catheterization [301, 359]. There is ample evidence that infection is much more likely to occur if there is obstruction to the outflow of urine. Mallory et al. (1940) induced partial ureteric obstruction and then injected bacillus coli intravenously into animals. They found that unilateral pyelonephritis occurred in 75 per cent of the injected animals and always involved the obstructed kidney. Bell (1942) made a corresponding observation. In experimental pyelonephritis Kennedy (1932) found that the lesions induced by the intravenous injection of organisms involve both cortex and medulla at an early stage, but when the infection is ascending, the renal pelvis is the part first involved. However, after 48 hours the kidney as a whole is affected, and then it is impossible from inspection of the kidney to discover in which way the organisms were introduced.

## Pathology

In chronic pyelonephritis there is usually some coarse scarring of the kidneys, but a somewhat similar appearance may be the result of arteriosclerosis. In chronic glomerulonephritis, however, the surface of the kidney shows granulation, but gross scarring is unusual. In mild cases of pyelonephritis the kidney tissue between the scars may be normal, even histologically; but in advanced pyelonephritis there is more loss of kidney substance and a decrease in kidney weight, which often affects the two kidneys unequally. Platt and Davson (1949) found that one kidney weighed at least twice as much as the other in 10 out of 14 instances, but in several other cases in his series the kidneys were not weighed.

Histologically, the lesions show extensive fibrosis with more or less preservation of renal tissue in the intervening portions. Periglomerular fibrosis is often encountered. Weiss and Parker (1939) describe a thyroid-like appearance due to the presence of dilated renal tubules which contain eosinophilic colloid casts. This they regard as characteristic of chronic pyelonephritis, and other writers concur [83]. Platt and Davson (1949) found this appearance to be present in 14 out of 26 of their autopsy cases. De Navasquez (1954) on the basis of serial sections, considers the dilatation to be due to intrarenal tubular obstruction, the result of the fibrosis.

The arterial and arteriolar changes are of great interest for, in



Fig VI 2a

Healed, recurrent acute pyelonephritis Hyperplastic arteriolosclerosis in scarred area X 550 (Weiss, S, and Parker, F, Jr, Medicine (Baltimore), 18, 221, 1939).

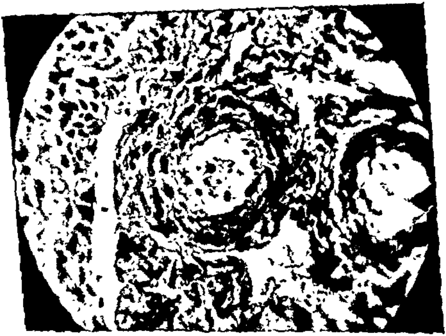


Fig VI 2b

Arteriole from same kidney as in Fig VI 2a but from nonscarred area Slight hyperplastic arteriolosclerosis X 550. (Weiss S, and Parker, F, Jr Medicine (Baltimore), 18 221, 1939)

the absence of hypertension, they may be confined to the affected parts of the kidneys. Even when "malignant hypertension" occurs in chronic pyelonephritis the characteristic arterial changes usually occur only in the kidneys, and the question arises whether the presence of the renal infection has modified the hypertensive changes in the arterioles. Weiss and Parker (1939) state that, irrespective of the presence of hypertension, the vascular lesions were most marked in the inflamed, scarred areas Fig. VI 2a and b hyperplastic arteriolosclerosis with intimal thickening was present in many of the cases, and in some cases arteriolonecrosis was present. Some of the arteriolar changes in scar tissue were purely involutionary, but this did not seem to apply to the hyperplastic arteriolosclerosis.

It is of great interest that the arteriolar changes in the patients without hypertension were identical with those encountered in hypertensive cases, but they were less severe and less extensive. Therefore, Weiss and Parker (1939) think that hyperplastic arteriolosclerosis and arteriolonecrosis may precede the hypertension, but subsequently are accelerated by it. In unilateral pyelonephritis cases, necrotizing arteriolitis was present on the affected side in six cases, but only on the unaffected side in two of these.

## Comment

Cases are seen at autopsy with gross scarring and great loss of renal tissue due to chronic pyelonephritis. Many of these patients have died from uraemia. In life, a high proportion of such severe cases exhibit the clinical manifestations of malignant hypertension, with obvious papilloedema, and a relatively high level of the diastolic pressure.

At autopsy, arterial lesions suggesting malignant hypertension may be encountered, but they are largely confined to the kidneys, and where only one kidney is affected with pyelonephritis, the arterial changes are likely to be restricted to, or much more prominent in, that kidney. Hence, the autopsy diagnosis of "malignant hypertension" on the basis of such findings cannot have the same significance as an autopsy diagnosis of "malignant hypertension" (malignant nephrosclerosis) made when the arterial changes involve both kidneys and are present in the arterioles of other organs

At the lower end of the severity scale it seems very likely that kidneys with scars due to the circumscribed healed lesions of chronic pyelonephritis are not associated with an increase in the incidence of hypertension above that of the general population. Such lesions do not lead to significant impairments of the excretory functions

*Cases of intermediate severity* are difficult. Unless many pieces of kidney are examined histologically, it may be impossible to determine the extent to which the kidneys are damaged. There is a rough relationship between the degree of atrophy and the weight of the

kidneys, but gross scarring does not necessarily lead to hypertension nor to much impairment of excretory functions. The question of how often chronic pyelonephritis causes hypertension remains unsolved. My impression is that there can be no simple answer to such a question. Just as there may be all grades of renal damage in pyelonephritis, so the expectation of a rise of blood pressure from chronic pyelonephritis may range from probable to improbable. Furthermore, the decision as to whether there has been an elevation of the blood pressure is not to be decided by selecting some blood pressure level above which

case, the final pressure may be regarded as normotensive and in the second case as hypertensive. Furthermore, in rereading the case histories of our patients, I found difficulty in selecting any single pressure which could be recorded as being characteristic, especially when there had been several admissions to hospital. My impression is that, in individual patients, the decision as to whether moderate blood pressure elevation is due to chronic pyelonephritis or to essential hypertension cannot usually be made confidently in the middle and later years of life. The problem, however, can be *approached statistically*, and with more knowledge than we now possess it may be practicable to estimate the probability of a moderate blood pressure rise being due to pyelonephritis.

## Renal Calculi

These may be uni- or bilateral, and may cause obstruction to the urinary outflow and lead to hydronephrosis and pyelonephritis. The obstruction may be continuous or intermittent. While hypertension

...ephritis is responsible. In some instances removal of a kidney which has been damaged by calculus may be associated with the return of the blood pressure to normal. Often, however, the fall of blood pressure is temporary and the blood pressure rises again within a few months after the operation. It is generally supposed that the blood pressure increase is the result of a Goldblatt mechanism, presumably from fibrosis in the damaged kidney. In younger people it is unusual to have very high blood pressures associated with renal calculus and in later years the hypertension may be coincidental.

## Prostatic and Urethral Obstruction

Maher and Wosika (1939) emphasize the importance of prostatic

is associated with elevation of the blood pressure, and relief of the obstruction with reduction of the blood pressure. It is often assumed that the blood pressure elevation is of renal origin but there is no proof of this and it may be reflex from distension of the bladder (Chapter VIII). In many instances the elevations of blood pressure are of moderate degree and an unimportant part of the clinical state.

Urethral obstruction may be associated with a blood pressure elevation which in some cases may be relieved surgically. Two such cases were described by Heintz et al. (1954b): one from hypospadias in a 12-year old boy and another from congenital urethral stenosis in a boy of 16 years.

## ACUTE GLOMERULONEPHRITIS

### Aetiology

The large majority of patients with glomerulonephritis have an *antecedent streptococcal infection occurring, as an average, three weeks* beforehand, sometimes a week earlier or later than this.

*Tonsillitis and other upper respiratory tract infections, sinusitis and* middle ear infections constitute the large majority of the primary lesions.

Other conditions not infrequently associated with the subsequent development of glomerulonephritis include scarlet fever, subacute bacterial endocarditis, various pyogenic infections, a variety of surgical conditions, pneumonia, influenza and occasionally such conditions as erythema nodosum and rheumatic fever.

There is some evidence that cold predisposes to nephritis. One possibility is that chilling of the body surface causes reflex vasoconstriction of the pharyngeal mucosa [246], and so renders the organism more susceptible to infection.

While other organisms may be concerned in the pathogenesis of acute glomerulonephritis, streptococci appeared to be easily the most important. It has been shown that certain types of streptococci, for example type 12 and type C 300 are of greater importance than others. Rammelkamp and Weaver (1953), Wertheim et al. (1953), Dingle et al. (1953) and Wilmers et al. (1954) found that a large proportion of attacks of acute glomerulonephritis follow infections of the throat with type 12 streptococci. In the first two references there are accounts of the extensive literature concerning the relationship of glomerulonephritis to infections. Infection with the streptococci of scarlet fever may lead to glomerulonephritis, but in recent years the incidence of glomerulonephritis in scarlet fever has diminished greatly. Rheumatic fever, however, although apparently due to streptococci, is seldom associated with glomerulonephritis. Glomerulonephritis may occur with infections by other streptococci, gonococci, meningococci, pneu-

mococci, influenza bacilli and possibly with many other organisms. I have seen a number of cases which followed acute appendicitis.

Epidemics of glomerulonephritis are not uncommon. During world war I trench nephritis, an epidemic form of acute glomerulonephritis, occurred in large numbers of soldiers who were exposed to cold in trench warfare Many patients made a complete recovery but a number developed advanced chronic nephritis and died from this cause.

A number of patients with focal nephritis are mistakenly diagnosed as acute glomerulonephritis. Attacks which appear to be identical with glomerulonephritis may arise in connection with sensitization phenomena and in the absence of any definite infection. Rytand et al. (1948), for example, described the occurrence of acute renal disease due to sensitization with poison oak and Shaffer et al. (1951) described glomerulonephritis resulting from sensitization to poison ivy. Various forms of anaphylaxis or drug sensitivity may be associated with a disorder resembling glomerulonephritis.

Ellis (1949) considers that acute nephritis represents the response of the kidney to an antigen immune body reaction. The reaction may be one of two distinct kinds: first, an anaphylactic response with vascular damage leading to acute glomerular nephritis or Ellis type 1 nephritis; second, a more insidious condition associated with increased glomerular permeability, a nephrotic condition, i.e. Ellis type 2 nephritis. Either of these conditions may lead on to chronic hypertensive Bright's disease, though it is less common in the latter disorder.

## Experimental Nephritis

A great variety of methods and toxic agents have been used to induce renal damage experimentally, including the administration of oxalates, uranium salts, mercurial salts, micro-organisms, bacterial products, antisera and the clamping of a renal artery for half an hour. Some of the more recent methods of inducing renal damage represent [illegible]
advance in that [illegible]
as it occ[illegible]
sensitivi[illegible]
injecting rat kidney s[illegible]
made in this way [illegible]
can be used to in[illegible]
experimental nepl[illegible] glomeruli are damaged [illegible]
[illegible]

[illegible] er-
[illegible] he
[illegible] a

[illegible] (1955) was able to cause profound renal ischaemia in rabbits by the intravenous injection of staphylococcal

toxin. The ischaemia was so striking for a time that injections of indian ink failed to enter the renal vessels. Various other methods have been used, such as the repeated injections of horse serum [151, 218]. Duval and Hibbard (1926a, b) produced glomerular damage by injection of living cultures of scarlatinal streptococci into rabbits which had been immunized.

## Pathology

Autopsy material indicates that at a very early stage of the disorder the glomeruli become filled with cells either as the result of cellular proliferation or from inflammatory infiltration. There is also oedema separating the capillary and epithelial basement membranes [178]. These changes lead to a degree of obstruction of the glomerular capillaries. This condition is widespread, involving most of the capillaries. The tubules, at this early stage, may be comparatively healthy, though casts and red cells may be present within them.

The condition may clear up quickly, or degrees of organization in the glomerulus may take place with the development of epithelial crescents in the capsules and other indications of chronicity.

## Renal Function

While the output of urine is diminished, the concentrating capacity is almost unimpaired in some cases of acute nephritis. In others the concentrating capacity is reduced. In the early stages of acute nephritis, there is usually a decrease in glomerular filtration [38, 103] and impairment of tubular functions may develop later. Potassium depletion occurs in some patients with acute glomerulonephritis, but it is uncertain whether this is due to decreased tubular absorption or increased secretion [101, 102]. Such changes are consistent with the belief that the primary lesions are mainly glomerular.

## Clinical Manifestations

The principle clinical features of acute glomerulonephritis include albuminuria, haematuria, oedema (usually involving the face as well as dependent parts), urinary casts (including blood casts), hypertension and decrease in the urinary output. Often there is pain in the lumbar region which may spread down and involve the genital region, and there may be dysuria. Fever, vomiting, diarrhoea and headaches may occur in some patients. An increase in blood volume [282] may be associated with distention of the neck veins and by the appearance of acute congestive heart failure; but neck vein engorgement may be present without heart failure. Occasionally, left ventricular failure with pulmonary oedema may occur. Encephalopathy of a type rarely encountered in essential hypertension is met, especially in the younger patients. It consists of convulsive attacks of an epileptiform type. The

convulsions may occur in the absence of uraemia and have become uncommon recently, presumably because of the prevalence of salt restriction.

The intensity of the clinical manifestations vary from case to case, and most of the clinical manifestations referred to may be present even to a striking degree, or entirely absent. The disorder may be so mild that it is only detected in the course of routine urine examinations following, for example, an infection such as scarlet fever. It must be assumed that many cases go undiagnosed and receive no medical attention. The patient in some instances may be unaware of any definite illness. Thus the condition may proceed unrecognized to complete recovery, or deteriorate, the first diagnosis made being chronic glomerulonephritis. In other instances the disease is one of obvious severity. A history of infection some few weeks beforehand is present in about 80 per cent of patients, the usual location being the upper respiratory region.

*Urinary findings*

Albuminuria. Usually there is a distinct cloud of albumin, occasionally the urine almost boils solid. In exceptional cases an illness may occur, with no albuminuria in the early stages, but otherwise identical with acute nephritis [6]. Examples of nephritis without albuminuria have been described in trench nephritis, the diagnosis in some such cases being verified at autopsy [75].

Haematuria often gives a slightly smoky appearance to the urine. In almost all cases of glomerulonephritis many red cells will be found in the urine when it is examined microscopically. While macroscopic haematuria often clears rapidly, an excess of red cells in the centrifuged deposit persists for weeks or months.

Urinary casts are almost always present, especially hyaline and blood casts. Epithelial casts are less frequently encountered. Granular casts are nearly always seen at a slightly later stage.

Oliguria is present in almost all cases. Occasionally there is anuria for one or more days but usually 200 to 600 ml. of urine per 24 hours is secreted Later, as oedema begins to clear there may be a diuresis.

*Oedema* may be mild or severe Sometimes there is no more than an increase in weight due to fluid retention; usually there is some bloating of the features but this may be recognizable only to those who already [illegible]
is prese[illegible]
nephrot[illegible] glomerulonephritis may supervene.

In some cases the retained fluid accumulates in the body [illegible]
peritoneum, pleura and [illegible]
in glomerulonephritis is [illegible]

at the lung bases and, exceptionally, frank pulmonary oedema may occur when acute glomerulonephritis is associated with left ventricular failure.

There is evidence that acute glomerulonephritis is associated with a general capillary damage, but it is sometimes stated that increased capillary permeability can only serve as an explanation for oedema when there is an increase of protein in the oedema fluid. I believe this reservation takes insufficient account of the likelihood that the rate of transit of water and salt through blood vessels can be increased without change in the permeability to protein. In the case of a dialysing membrane impermeable to protein but permeable to water and salts, it is obvious that the rate of transit of fluid through several thicknesses of membrane is less than through a single layer. It seems very likely that increase in the permeability of vessels to water and salts may occur in the absence of increased permeability to protein. Fishberg (1954) considers that in some instances oedema may be present in acute glomerulonephritis before there is time for any appreciable sodium retention. The occurrence of substantial oedema, however, requires the retention of water and salt.

*Hypertension.* — The blood pressure is usually raised in acute glomerulonephritis but the level does not often exceed 185/125. The increase may be as little as 10 to 20 mm. systolic, 10 mm. diastolic, and the actual blood pressure may remain within the conventional limits of "normal". Very high blood pressures usually indicate that the condition is an acute exacerbation of a chronic nephritis.

In acute cases the level of the blood pressure, even at its peak, seems insufficient to explain why acute congestive heart failure occurs as a complication of acute nephritis. There is, however, an additional factor which adds to the cardiac overload, namely, the increase in the blood volume.

According to Dexter and Haynes (1944) renin was detected in one patient with acute glomerulonephritis but not in others. Arneil and Dekanski (1954) also claim that they have been able to demonstrate the presence of vasopressor activity in the plasma of children with acute nephritis. They find that the pressor activity of the plasma is not blocked by dibenamine and is therefore unlikely to be due to adrenaline, noradrenaline, tyramine or nicotine It compares well in properties with angiotonin.

Wilson (1953) considers that the morphological appearances in acute glomerulonephritis suggest that renal ischaemia brought about by pathological changes in the glomeruli is responsible for the blood pressure elevation.

*Retinopathy.* In acute glomerulonephritis it is unusual to observe significant changes in the blood vessels or star-shaped macular figures of hard exudates Retinal haemorrhages may occur and, when there is

... With the possible ... robably secondary to the hypertension

*Cardiac embarrassment.* A degree of enlargement of the cardiac silhouette may occur in acute glomerulonephritis from combinations of cardiac dilatation and pericardial effusion. After one or two months left ventricular hypertrophy may be found in autopsy cases. Direct damage of the myocardium is probable, and this, combined with ... blood volume and blood pressure, leads to heart failure. ... failure may ...

veins may be present without evidence of heart ... to increase of blood volume. The electrocardiographic signs are not definite enough to aid the distinction between acute nephritis and acute exacerbations of chronic nephritis. Low or inverted T waves and elevation or depression of the ST segments may occur in acute as well as in chronic glomerulonephritis.[71]

*Encephalopathy.* — Since the introduction of salt free diets, convulsive episodes have become comparatively uncommon in patients with acute nephritis. In the days before salt restriction epileptiform attacks were not uncommon in young patients with nephritis. It has been my impression that these convulsive episodes are not due solely to hypertension, for in essential hypertension they are rare, even in patients who consume average amounts of salt In acute nephritis, attacks may occur in the absence of important degrees of nitrogen retention but usually hypertension is present to some degree Other ...

... in the absence of nephritis.

*Course of acute glomerulonephritis.* — In a majority of cases there is complete resolution. The mortality in the acute stage has been variously estimated as between 3 and 12 per cent ... ber become chronic Accordi...

... may occur even when they have been chronic for a year or two[180]. There may be a residual hypertension very similar to essential hypertension

## DISORDERS EXHIBITING THE NEPHROTIC SYNDROME

In general, the term nephrotic syndrome is applied to disorders with gross albuminuria, hypoproteinaemia and oedema. There is good evidence that the syndrome may occur in a variety of disorders:

amyloid disease, toxic nephroses, true lipoid nephrosis, glomerulonephritis, Kimmelstiel-Wilson disease, disseminated lupus erythematosus and renal vein thrombosis. Many, probably all, of these conditions may be associated ultimately with hypertension.

## Amyloid Disease

Amyloid disease of the kidney may cause a nephrotic syndrome which may therefore arise in chronic tuberculosis and in chronic suppurative diseases. Amyloid is deposited in the region of the basement membrane of the glomerular capillaries, fibrosis occurs, and eventually the condition may become indistinguishable from chronic glomerulonephritis. Albuminuria may be the only renal manifestation but in some patients this is considerable, causing hypoproteinaemia and massive oedema involving the face and dependent parts. Sometimes fluid accumulates in the peritoneal, pleural and even pericardial cavities. Later there may be renal insufficiency and hypertension, no doubt due to impaired circulation through the glomeruli. Combinations may occur of the nephrotic syndrome, renal insufficiency and hypertension, which markedly resemble the nephrotic type of chronic glomerulonephritis. The diagnosis may be made by the Congo red test for amyloid and biopsy.

## Toxic Nephroses

Infections and drugs may cause albuminuria but only rarely a nephrotic syndrome. The condition may clear when the toxic agent is removed. Such renal impairments have occurred with poisoning by mercury and bismuth salts, oxalates, organic arsenic compounds and gold salts. Occasionally infections such as diphtheria and typhoid fever cause a similar condition.

In severe cases there may be oliguria or anuria. The non-protein nitrogen may rise rapidly; oedema may be present but is seldom extensive; the blood pressure may or may not be raised to levels such as 160/95 but hypertension is seldom a striking feature of the illness. The urine flow may be re-established with relief of symptoms, but in some cases anuria persists or the volume of urine remains at a low level, the non-protein nitrogen rises to high figures and uraemia supervenes. At this stage encephalopathic fits may occur when the blood pressure is not excessively high. Recovery of renal function is usual in the patients who survive.

## "Genuine Lipoid Nephrosis" and the "Nephrotic Type of Glomerulonephritis"

It is generally agreed that there is a disorder of unknown origin in which profuse albuminuria is associated with the insidious development of generalized oedema often of high degree, not infrequently associated

with the accumulation of fluid in the visceral cavities. It is also generally agreed that a clinical picture which superficially resembles this may be encountered in patients who give a clear-cut history of an antecedent nephritis

*The clinical features* characterising the early stages of lipoid nephrosis are widespread oedema, hypoproteinaemia, alteration in the albumin-globulin ratio, general tiredness, anaemia and susceptibility to infection. At this stage patients may die from intercurrent infection, may recover to a stage where albuminuria only is present, or may recover completely. Recurrences are more frequent when there is residual albuminuria. I have, however, observed a recurrence after albuminuria has cleared completely for a period of several weeks. Accumulations of fluid may be present in the visceral cavities and there may be basal râles. Barness et al. (1950) studied 208 patients with the nephrotic syndrome in the children's hospitals of Boston. No constitutional disturbance was observed to take place before the onset of the nephrosis About half of the patients recovered completely without residual disease.

The outlook is better when the clinical picture is one of "pure" lipoid nephrosis than when it resembles the nephrotic type of glo-

22 death
nephritis
There ... 48.8 per cent for chronic
nephri

The ... lipoid nephrosis seems to have become a little less obscure in the last ...
of glomerulo
both may re... upon the kidneys of an immunological response In animals, by varying experimental conditions, it is possible to induce disorders which resemble either nephrosis or nephritis. It seems almost certain that, in man, more than one antigen has the capacity to cause nephrosis and nephritis.

*Clinically*, there are patients whose manifestations seem to bridge the gap between pure lipoid nephrosis and the nephrotic type of glomerulonephritis. It is possible, but not proved, that the basic pathologies of the disorders have some features in common

Albuminuria may, theoretically, be due to loss from the ...
or decreased absorption ...
is that
meable

Lauson et al (1954) studied the simultaneous renal clearances of the colloid dye T-1824 and of albumin in patients with the nephrotic

syndrome. The authors found evidence of increased glomerular per meability in the nephrotic syndrome. The favourable effects of treat ment with ACTH were due to a return of the permeability toward normal. Chinard et al. (1954) also concluded that proteinuria in th nephrotic syndrome is due to increased permeability of the glomeruli

The thickenings of the basement membrane of glomerular capillarie in at least some cases of lipoid nephrosis should be considered in relatior to studies of glomerular filtration. The observations of Bruck et al (1954) are of interest in this connection. These authors made 10( clearance tests in 45 children with the nephrotic syndrome. In the patients who did not appear to be developing glomerulonephritis the glomerular filtration rate and the filtration fraction were usually normal, or about normal, but patients with or who later developed glomerulonephritis showed a reduction in the glomerular filtration rate.

Additional information, relating mainly to the oedema characteristic of the nephrotic syndrome, is to be found in Symposia published in the Journal of Clinical Investigation, April, 1954 and in the American Journal of Medicine, February, 1955.

*Relationship of "lipoid nephrosis" and the "nephrotic type of glomerulonephritis".* — The nature of the relationship between the above named clinical conditions is disputable. While some authors regard these conditions as separate disorders, others believe that they are manifestations of a single underlying pathology. It is generally agreed that in the cases ordinarily described as lipoid or idiopathic nephrosis, the onset of albuminuria, oedema and other symptoms is insidious; and although in a few cases there is a history of antecedent infection, most patients give no such history. Evidence favouring a non-streptococcal origin of many nephroses comes from Rytand et al. (1948) who found the anti-streptolysin titre raised in nephritis but low in nephrosis due to poison oak dermatitis. Classical examples of idiopathic or lipoid nephrosis exhibit no haematuria, no impairment of renal excretory function and no hypertension. Such cases usually assume a chronic course extending over several months or years, but a proportion of cases recover, especially the children, and may leave behind no residue of haematuria, hypertension or other clinical manifestation. Some patients in a late stage develop renal insufficiency and hypertension and resemble closely or become indistinguishable from the class of patients usually regarded as examples of the nephrotic type of glomerulonephritis. There is much dispute about patients who follow this course. Some regard such changes as being compatible with a diagnosis of lipoid nephrosis, being the consequence of interference with the glomerular circulation brought about by thickening of the basement membrane of glomerular capillaries, a lesion thought by some to be characteristic of lipoid nephrosis. Others regard nitrogen retention or a rise of blood

pressure as indications that a diagnosis of lipoid nephrosis was mistaken. In recent years, especially, there has been a tendency to regard lipoid nephrosis and the nephrotic type of glomerulonephritis as somewhat different manifestations of a common basic pathology.

Ellis (1942) refers to a type 2 nephritis which includes the classical lipoid

that the tendency to the subsequent development of renal function defects or

Dawson

of nephr

nephritis

cases fin

are not

According to Bell (1938), examples of lipoid nephrosis may be encountered in which thickenings of the capillary basement membranes

He also refers to lobular glomerulonephritis in more fulminant cases in which the glomerulus becomes

tubule impairment plays a part in the development of nephrosis, and considers that albuminuria is not the sole explanation of the syndrome

If we accept Fahr's concept of the nephroses, we see that in the advanced stages neither hypertension, nor impairment in concentrating capacity of the kidneys, can be used as a means of distinguishing between nephrosis and glomerulonephritis However, the early incidence of these is in favour of glomerulonephritis, their late development

caused by the pathological generalized oedema is common to both.

As already stated, some examples of hypoproteinaemia with chronic renal

oedema are manifestly due to glomerulonephritis, the evidence being a clear-cut antecedent history of acute nephritis, oedema developing later, no doubt as a result of profuse albuminuria. In other instances a similar condition develops insidiously with no antecedent history of acute nephritis, but the presence at an early stage of haematuria, impairment in the concentrating capacity of the kidneys, or the presence of hypertension, suggests that the condition is glomerulonephritis.

*Summary. — It has not yet been decided whether the difficulty in distinguishing between some cases of lipoid nephrosis and the nephrotic type of glomerular nephritis is diagnostic, or whether the difficulty is that no boundary exists, and they are aspects of a single basic pathology. Certainly patients who, in the early stage, are examples of classical lipoid nephrosis may later develop impairment of renal functions and hypertension. The hypertension which develops seems to be a renal hypertension and the demonstration of thickening of the capillary basement membrane in glomeruli and subsequent fibrotic changes would seem to afford an explanation in terms of renal ischaemia.*

## The Kimmelstiel-Wilson syndrome

The Kimmelstiel-Wilson (1936b) syndrome is of particular interest in relationship to hypertension, in that it is a non-inflammatory disorder associated with histological changes in the glomeruli, which lead to hypertension in a large proportion of cases; 88 per cent according to Clark and Skillern (1955). The disorder usually occurs in patients with diabetes of many years' duration, and most eventual deaths are from renal and cardiovascular complications. The occurrence of these complications is not restricted to patients with advanced diabetes, or to poorly controlled patients; they occur in mild and in well managed cases. The incidence of renal and cardiovascular complications seems to depend more upon the duration of the diabetes than upon its severity.

Where diabetes begins early in life arteriosclerotic renal changes and hypertension may occur at an early age. Some of these patients show a definite interference with renal excretory functions In a series of 30 autopsies Martensson (1949) found the Kimmelstiel-Wilson lesion in 7 cases.

The essential lesion appears to be a hyaline thickening of the basement membrane of glomerular capillaries together, in many instances, with hyaline nodules in the glomerular tufts. Arteriolosclerosis is present in most cases and there is usually advanced atheroma of the renal artery. Lipoid deposits and cloudy swelling occur in the tubule cells. The appearance of the glomeruli suggests that renal ischaemia may explain the rises of blood pressure which occur eventually in most of these patients [111a, 127]. On occasion malignant hypertension may develop In some instances the main clinical manifestation is albuminuria, which may lead to an advanced state of nephrotic oedema.

# CHRONIC GLOMERULONEPHRITIS

## Aetiology

Ellis (1942) considers that chronic hypertensive Bright's disease is a hotch-potch of various renal disorders including late stages of his

used here as part of a simple classification of nephritis cases into acute, subacute and chronic, but it is not intended to include under this heading cases of pyelonephritis, malignant hypertension, chronic nephrosis or the nephrotic type of glomerulonephritis. Using the term in this way, chronic glomerulonephritis may occur in children or in adults. In some instances, more particularly in children, there may be a history of one or more than one attack of acute glomerulonephritis and often the transition to chronic nephritis occurs without an intermediate period of apparent recovery. Alternatively, a latent period of many years intervenes between an acute attack and the eventual development of chronic glomerulonephritis.

th:

pa ... scarlet fever or streptococcal sore throats, the appearance in the urine of albumin, red cells and casts may be found at a routine

suggestion

with advan ... nephritis give no indication in their previous history of an acute episode.

In many cases of chronic nephritis there occur a number of acute exacerbations in which the albumin, red cells and the number of casts in the urine increase According to Seegal et al (1940) the interval between an infection and an exacerbation may be as short as 1 to 4 days. This may help to distinguish such exacerbations from a first attack of glomerulonephritis. During acute exacerbations a compensatory diuresis may be diminished and the patient's condition is temporarily or permanently impaired. The question ...

whether ...

is due to

or wheth

course ev

... of acute exacerbations. In some patients infections such as tonsillitis are ...

changes ...

rises

oedema are manifestly due to glomerulonephritis, the evidence being a clear-cut antecedent history of acute nephritis, oedema developing later, no doubt as a result of profuse albuminuria In other instances a similar condition develops insidiously with no antecedent history of acute nephritis, but the presence at an early stage of haematuria, impairment in the concentrating capacity of the kidneys, or the presence of hypertension, suggests that the condition is glomerulonephritis.

*Summary. — It has not yet been decided whether the difficulty in distinguishing between some cases of lipoid nephrosis and the nephrotic type of glomerular nephritis is diagnostic, or whether the difficulty is that no boundary exists, and they are aspects of a single basic pathology. Certainly patients who, in the early stage, are examples of classical lipoid nephrosis may later develop impairment of renal functions and hypertension. The hypertension which develops seems to be a renal hypertension and the demonstration of thickening of the capillary basement membrane in glomeruli and subsequent fibrotic changes would seem to afford an explanation in terms of renal ischaemia.*

## The Kimmelstiel-Wilson syndrome

The Kimmelstiel-Wilson (1936b) syndrome is of particular interest in relationship to hypertension, in that it is a non-inflammatory disorder associated with histological changes in the glomeruli, which lead to hypertension in a large proportion of cases; 88 per cent according to Clark and Skillern (1955). The disorder usually occurs in patients with diabetes of many years' duration, and most eventual deaths are from renal and cardiovascular complications. The occurrence of these complications is not restricted to patients with advanced diabetes, or to poorly controlled patients; they occur in mild and in well managed cases. The incidence of renal and cardiovascular complications seems to depend more upon the duration of the diabetes than upon its severity.

Where diabetes begins early in life arteriosclerotic renal changes and hypertension may occur at an early age. Some of these patients show a definite interference with renal excretory functions. In a series of 30 autopsies Martensson (1949) found the Kimmelstiel-Wilson lesion in 7 cases.

The essential lesion appears to be a hyaline thickening of the basement membrane of glomerular capillaries together, in many instances, with hyaline nodules in the glomerular tufts. Arteriolosclerosis is present in most cases and there is usually advanced atheroma of the renal artery. Lipoid deposits and cloudy swelling occur in the tubule cells. The appearance of the glomeruli suggests that renal ischaemia may explain the rises of blood pressure which occur eventually in most of these patients [111a, 127]. On occasion malignant hypertension may develop. In some instances the main clinical manifestation is albuminuria, which may lead to an advanced state of nephrotic oedema.

# CHRONIC GLOMERULONEPHRITIS

## Aetiology

Ellis (1942) considers that chronic hypertensive Bright's disease is a hotch-potch of various renal disorders including late stages of his

used here as part of a simple classification of nephritis cases into acute, subacute and chronic, but it is not intended to include under this heading cases of pyelonephritis, malignant hypertension, chronic nephrosis or the nephrotic type of glomerulonephritis. Using the term in this way, chronic glomerulonephritis may occur in children or in adults. In some instances, more particularly in children, there may be a history of one or more than one attack of acute glomerulonephritis and often the transition to chronic nephritis occurs without an intermediate period of apparent recovery. Alternatively, a latent period of many years intervenes between an acute attack and the eventual development of chronic glomerulonephritis.

The initial attack may be mild and, indeed, it is generally recognized that such mild attacks may pass unrecognized. In the investigation of patients with scarlet fever or streptococcal sore throats, the appearance in the urine of albumin, red cells and casts may be found at a routine examination and be accompanied by minimal symptoms or no symptoms, suggesting that larval forms of acute glomerulonephritis occur. On this basis there are those who feel that chronic glomerulonephritis always arises from

sugges

with a

previo ... of acute episode,

According to Seegal et al. (1940) the interval between an infection and an exacerbation may be as short as 1 to 4 days. This may help to distinguish such exacerbations from a first attack of glomerulonephritis. During acute exacerbations a compensatory diuresis may be diminished and the patient's condition is temporarily or permanently impaired. The question has arisen of whether the advancing

is due to a series of a

or whether chronic g

course even without ... of acute exacerbations. In some patients infections such as tonsillitis are associated with urinary changes suggesting exacerbations of activity. When the blood pressure rises the development of secondary changes in arteries and arterioles

adds a factor which may cause further loss of renal function. My own impression is that chronic glomerulonephritis may arise directly out of acute glomerulonephritis or may develop insidiously, with or without recognized episodes of acute exacerbation.

## Pathology

The contracted granular kidneys of advanced chronic glomerulonephritis often weigh less than 40 gm. each. The surface granules are fine or of intermediate size, but there may be coarse scars of the arteriosclerotic type. The cortex is much narrowed and the distinction between cortex and medulla is often indefinite. In patients dying at an early stage the kidneys, however, may be large and pale, even in patients exhibiting no nephrotic syndrome.

The glomeruli are always involved. Some are converted into hyaline masses surrounded by connective tissue, and are evidently functionless. The damaged glomeruli may show fibrosis between the capillary loops and much cellular increase. Many of the capillaries will be obstructed and the circulation of blood through a glomerulus may be arrested or restricted to a part of the glomerulus. In addition, even in chronic cases, an appearance more characteristic of subacute glomerulonephritis may be found, namely, crescents of epithelial cells in the glomerular capsule, leading to compression of the glomerular tuft. Not all glomeruli are so affected. Fibrosis is dense in the parts of the kidney with no functioning tissue but dilated tubules are to be found between bands of fibrous tissue. Some of the tubules are connected with functionless glomeruli and the extent to which these tubules may exhibit residual activity is a topic of speculation. In certain fishes the kidneys perform their function in the absence of glomeruli, so one may suppose a residual function is not impossible in man.

In most chronic cases the main renal arteries show arteriosclerosis. The media of arterioles often exhibit medial hypertrophy, whereas, in essential hypertension the arterioles often show atrophic changes. In malignant hypertension, however, medial hypertrophy may be present. Arteriolosclerosis with elastic tissue reduplication may be present in nephritis as in patients with essential hypertension. In addition, there may be an obliterative endarteritis, the intima being thickened diffusely by deposits of connective tissue which contain little or no elastic tissue. This change may be secondary to loss of renal parenchyma. In situations other than the kidney, arteries may be closed by endarteritis if there is peripheral obstruction to the flow of blood, or if there is atrophy of the parenchyma which such arteries normally supply.

Of great interest is the association of nephrocalcinosis with glomerulonephritis, and the contention of Arons et al. (1955) is that those cases in which the calcium is confined to the cortex are, in all pro-

bability, secondary to glomerulonephritis; whereas primary calcinosis leads to a more marked deposition in the medulla. Renal insufficiency with hypertension may be secondary to nephrocalcinosis due to hyperparathyroidism, or excessive milk and alkali intake (McQueen, 1952, Kessler, 1955).

## Renal Function

In hypertension a study of the renal concentrating capacity should always be made. The maximum specific gravity is of value. Where there is a severe impairment of the concentrating capacity of the kidneys, the specific gravity may be fixed in the region of 1.010. It is important that the specific gravity should be measured with an accurate hydrometer and that the temperature of the urine should be at the calibration temperature of the hydrometer; or if the urine temperature is much above or below this temperature, a correction may be made by adding 0.001 for every 3 degrees Centigrade above and deducting 0.001 for every 3 degrees Centigrade below the temperature for which the hydrometer is calibrated. The urea clearance test is of value, but only if no pre-renal factors are reducing the clearance of urea. The usual interpretation is that when the urea clearance is 70 per cent or more of the average normal the kidneys are excreting urea satisfactorily. Mild impairments have clearances of 40 to 70 per cent of normal, moderate impairments have 20 to 40 per cent of normal and severe impairments of renal function may be 20 per cent of normal or less. As a routine test in hypertensive patients I prefer the urea concentration test of McLean, in which 15 gm. of urea in 100 ml. water are administered on an empty stomach after 10 hours' fasting from food and fluid The maxim[illegible]
passed at hourly inte[illegible]
be 2 per cent or mor[illegible]
siderable impairment[illegible]
but not [illegible]
blood is [illegible]
the non-[illegible] [illegible] whether a compensatory diuresis is enabling an adequate urinary excretion to take place. The normal range of the non-protein nitrogen of the blood is 20 to 40 mg. per 100 ml

In chronic glomerulonephritis the chief impairment is a reduction in the glomerular filtration rate Later, tubular damage outstrips glomerular damage [100].

Disturbances in the potassium metabolism occur frequently in terminal nephritis There may be retention [106, 179] or hypopotassaemia [64, 78, 190] Those interested in the subject should [illegible]
aldoster[illegible]

et al. (1944). In such cases as much as 15 to 20 gm. of sodium chloride daily may be needed to prevent salt depletion.

## Clinical Manifestations

As indicated in the previous section, some patients with a nephrotic syndrome have degrees of renal insufficiency and of hypertension. Apart from the presence of oedema, such patients pursue a course very similar to that of patients with chronic glomerulonephritis who are not oedematous. It is sometimes overlooked that oedema and nitrogen retention represent essentially the results of certain changes in renal function. It does not follow that the aetiology and pathogenesis are the same in all patients exhibiting such changes.

The need to discuss whether "nephrosis" is an entity distinct from the "nephrotic type of glomerulonephritis" made it preferable to treat the latter topic in the preceding section. It would otherwise have been equally appropriate to describe the disorder in the present section. A history of antecedent acute glomerulonephritis or of a stage with nephrotic oedema, is obtainable in less than half of the cases, in my experience.

*Urinary findings.* — Occasionally there is little more to indicate renal damage than albuminuria and a few red cells and casts in the urine. The concentrating capacity and the urinary output may be natural. In such patients there may be few symptoms apart from general lassitude.

In acute exacerbations of chronic nephritis, urinary albumin, red cells and casts are usually increased and there is a temporary decrease in the urinary output. Much albumin may be present in the urine in the cases where there is also nephrotic oedema.

In advanced cases of chronic glomerulonephritis there may be little albuminuria and only a few red cells and casts in the urine, but the maximum urinary specific gravity may not exceed 1012. The output of urine may be increased to compensate for the diminished concentrating power, and the night urine is particularly increased. Where there is no compensatory diuresis the patient is likely to show nitrogen retention.

*Oedema.* — This is usually slight in the absence of congestive heart failure. Many patients who have nephrotic oedema in the subacute stage lose their oedema as the disorder becomes chronic. This, however, is not an invariable occurrence and considerable oedema of renal distribution may be present even in the last stages of chronic glomerulonephritis Even when oedema is slight elsewhere, the eyelids are sometimes a little puffy.

*Retinopathy.* — There is good evidence that the retinal changes in advanced chronic nephritis are largely dependent upon blood pressure elevation. All the retinal changes encountered in essential hypertension

are met in chronic nephritis. Furthermore, it has been our experience in Dunedin that in nephritis as in essential hypertension, given time, all exudative changes may be expected to be dispersed completely if the blood pressure is maintained at satisfactory levels by methonium salts or by other effective hypotensive agents. The exudative changes referred to are haemorrhages, star-shaped macular figures of hard exudate, soft fluffy exudate, retinal oedema and papilloedema. Local arterial changes are also encountered but these certainly persist in most, probably in all, cases. Probably the relatively high diastolic pressures and the high basal pressures encountered in chronic nephritis explain why such patients are especially likely to exhibit exudative retinal changes When the blood pressure has been maintained at a near to normal level, patients may die in uraemia with no exudative signs in the retinae; but in patients with much nitrogen retention haemorrhages and exudates sometimes occur even when the blood pressure is well controlled.

*Hypertension* — All of the various clinical manifestations of hypertension described in essential hypertension occur in advanced chronic nephritis and relief is obtained in much the same way by *effective blood* pressure reduction Complications of hypertension, such as cerebral haemorrhage and thrombosis, also occur as in essential hypertension The blood pressure in exceptional cases, usually the mild ones, may be normal In advanced cases there may be considerable hypertension and the diastolic pressures are usually high in relation to the systolic pressures. A characteristic blood pressure in severe essential hypertension is 250/135 and in advanced chronic nephritis 240/160 For equal levels of the casual blood pressures the basal pressures are usually higher in advanced nephritis than in essential hypertension [128] Usually patients with severe defects in the excretory capacities of the kidneys have high blood pressures but there is no exact parallelism, and sometimes patients with satisfactory excretory functions have very high blood pressures.

The reactivity of the blood pressure to the cold pressor test and to the blood pressure raising reflex from muscle [3] is in our experience less, as an average, in advanced chronic nephritis than in essential hypertension [4].

It is generally considered that the rise in blood pressure is due primarily to constriction of arterioles. Unlike the very early stage of acute nephritis, chronic nephritis appears to be unassociated with consistent changes in the plasma volume (Steinbeck, 1953) and substantial increases, when they occur, appear to be explained by anaemia

Patients with advanced chronic nephritis [illegible]
methon[illegible]
hy[illegible]

et al. (1944). In such cases as much as 15 to 20 gm. of sodium chloride daily may be needed to prevent salt depletion.

## Clinical Manifestations

As indicated in the previous section, some patients with a nephrotic syndrome have degrees of renal insufficiency and of hypertension. Apart from the presence of oedema, such patients pursue a course very similar to that of patients with chronic glomerulonephritis who are not oedematous. It is sometimes overlooked that oedema and nitrogen retention represent essentially the results of certain changes in renal function. It does not follow that the aetiology and pathogenesis are the same in all patients exhibiting such changes.

The need to discuss whether "nephrosis" is an entity distinct from the "nephrotic type of glomerulonephritis" made it preferable to treat the latter topic in the preceding section. It would otherwise have been equally appropriate to describe the disorder in the present section. A history of antecedent acute glomerulonephritis or of a stage with nephrotic oedema, is obtainable in less than half of the cases, in my experience.

*Urinary findings.* — Occasionally there is little more to indicate renal damage than albuminuria and a few red cells and casts in the urine. The concentrating capacity and the urinary output may be natural. In such patients there may be few symptoms apart from general lassitude.

In acute exacerbations of chronic nephritis, urinary albumin, red cells and casts are usually increased and there is a temporary decrease in the urinary output. Much albumin may be present in the urine in the cases where there is also nephrotic oedema.

In advanced cases of chronic glomerulonephritis there may be little albuminuria and only a few red cells and casts in the urine, but the maximum urinary specific gravity may not exceed 1012. The output of urine may be increased to compensate for the diminished concentrating power, and the night urine is particularly increased. Where there is no compensatory diuresis the patient is likely to show nitrogen retention.

*Oedema.* — This is usually slight in the absence of congestive heart failure. Many patients who have nephrotic oedema in the subacute stage lose their oedema as the disorder becomes chronic. This, however, is not an invariable occurrence and considerable oedema of renal distribution may be present even in the last stages of chronic glomerulonephritis. Even when oedema is slight elsewhere, the eyelids are sometimes a little puffy.

*Retinopathy.* — There is good evidence that the retinal changes in advanced chronic nephritis are largely dependent upon blood pressure elevation. All the retinal changes encountered in essential hypertension

disturbing the fluid balance, may lead to further nitrogen retention and sometimes to a terminal uraemia.

Nitrogen retention leads to increasing lassitude and anaemia. The anaemia is predominently due to suppression of erythropoiesis [204] but at times it may be definitely haemolytic. Loss of appetite, vomiting, diarrhoea, sweating and dryness of the mouth may occur; there is an increased liability to convulsive attacks of an epileptiform character and, quite apart from this, small twitching movements of the fingers, toes and arms may be observed. These latter, it is said, are due to reductions in the blood calcium and may be prevented by the administration of calcium. They are, however, of very bad prognostic significance. In some instances a patient may be restored temporarily to a satisfactory condition or to a condition of comparative comfort, even permitting a certain amount of work. In others, further ground is lost, the non-protein nitrogen rises further, the patient becomes drowsy and finally dies in uraemic coma.

### Renal Dwarfism

Renal "dwarfism", "infantilism", or "rickets", occurs usually in children who have renal insufficiency from chronic nephritis, hydronephrosis or pyelonephritis or other cause. In 1884 Davies-Colley described a girl of 13 with rickets which was unresponsive to cod liver oil and was associated with gross bilateral hydroureters and calculi. Morley Fletcher in 1911 and Parsons in 1911 described the condition and in 1932 Maddox reviewed 84 cases from the literature. The condition is almost always associated with renal function impairment and polyuria. There is fibrosis of the kidneys, sometimes with calcification of arteries Decalcification and some deformity of bones is usual and metastatic calcification is frequent.

The blood pressure may be elevated though hypertension was present in only 9 out of 30 cases reported by Maddox in which the blood pressure was measured. Joiner and Thorne (1953) made the suggestion that this may be explained in some patients by lowering of the blood sodium.

## THE ENDOCRINE GLANDS IN RELATION TO HYPERTENSION

### Pituitary Hormones

The posterior pituitary hormones are unlikely to be concerned in the mechanism of hypertension for long before they produce any appreciable increase in the blood pressure they cause anti-diuresis and a striking pallor

There is no striking relationship between disorders of the anterior part of the pituitary gland and hypertension. Many patients with

pressure increase must be neurogenically maintained in the sense that when the nervous impulses are blocked, great falls of blood pressure occur, even in the horizontal posture. This might be explained either by the presence of sympathetic overactivity or by increase in the reactivity of blood vessels to neurogenic impulses.

It is generally assumed that the hypertension of chronic nephritis is of renal origin and that it bears a close relationship to other forms of renal hypertension which occur in man, and to the Goldblatt type of experimental hypertension in animals. The histological evidence suggesting impaired renal circulation favours this [357]. As indicated elsewhere (Chapter IX) it seems likely that Goldblatt hypertension involves not only a renin-angiotonin type of mechanism, but also an extra-renal component, best seen in experimental renoprival hypertension. Direct evidence is lacking of a relationship between experimental renal hypertension and the hypertension of advanced chronic nephritis; but we know of no reasonable alternative explanation.

*Congestive heart failure.* — In some cases the heart failure of chronic nephritis is due mainly to hypertension, but in others the retention of nitrogenous waste products is likely to impair the action of the heart muscle and probably is important also.

In patients who depend upon a compensatory diuresis for the adequate excretion of waste products, the oliguria of heart failure may be disastrous. Even so, the chance of successful therapy is much better than when the oliguria is due to a substantial acute exacerbation, for in heart failure the use of digitalis and judicious blood pressure reduction may permit re-establishment of an adequate output of urine. Pericardial effusions are not uncommon in advanced nephritis. In cases with left ventricular failure cardiac asthma or pulmonary oedema may occur. Electrocardiograms and x-rays are likely to reveal evidence of left ventricular hypertrophy. Where uraemia is present the disturbances of potassium metabolism may be reflected in the electrocardiogram.

*Nitrogen retention and uraemia* — In general, patients with advanced chronic glomerulonephritis, with compensatory increases of urine output, may have very few symptoms apart from lassitude and the symptoms arising from any hypertension which is present. While such patients may be comparatively well or even, on occasion, capable of living a full life, they may be precipitated into uraemia by intercurrent infection, congestive heart failure, or by an acute exacerbation of the nephritis.

Alternatively, the renal function may deteriorate slowly until the blood non-protein nitrogen remains elevated, despite curtailment of the protein intake to 30 or 40 gm. daily. Vomiting or diarrhoea, by

maintain homeostasis, but Haimovici (1948) has suggested that the sweat glands in man have an adrenergic supply.

Advanced retinal changes may occur sometimes. Gutman (1947) described a case of phaeochromocytoma causing malignant hypertension, papilloedema and retinal exudates, and leading to uraemia and death. Spalding (1947) and Rodin (1945) described phaeochromocytomas with grade 3 retinal changes which cleared after successful operation; and Richardson et al. (1955) and Sowry (1956) described reversal of grade 4 retinal changes.

Paroxysmal attacks of hypertension may occur spontaneously as the result of emotion or if the phaeochromocytoma is palpated or deliberately massaged or handled at an operation. Attacks are also induced by diagnostic procedures which will be mentioned later. It has been recognized for some time, however, that not all patients with phaeochromocytoma exhibit paroxysmal [illegible]
may be assumed to be ess[illegible]
tion, operation or autops[illegible]
[213, 282, 331, 353]. Green (1946) was impressed by the frequency with which patients with phaeochromocytoma developed a chronic, persistent hypertension and various secondary changes. He made an analysis of 50 cases from the literature. Of the 37 of these who were chronically hypertensive 4 exhibited a malignant hypertension, 20 at times had albuminuria, 11 had decreased excretion of phenolsulphonphthalein and 2 had azotaemia. Of 16 chronically hypertensive patients who came to autopsy, mild to severe nephrosclerosis was present in 7. There seems to be good evidence that this form of hypertension may lead on to secondar[illegible]

Green [illegible]
in the c[illegible] of a tumour causes a fall in the resting blood pressure to normal levels in almost every case. He thinks, therefore, that even [illegible]
mediated by a humo[illegible]
suggest the develop[illegible]
through the [illegible]
chanism ass[illegible] sclerosis. Goldenberg et al. (1950), however, postulate the development of a self-perpetuating mechanism as a late result of phaeochromocytoma on the basis of a degree of persistence of the hypertension following the operation.

Smithwick et al. (1950) described a series of 11 patients with phaeochromocytoma and only 4 exhibited paroxysmal attacks. The diagnoses in this series were often made during a surgical exploration. Pre-operative diagnoses are made more readily in paroxysmal cases, but in recent years, with improved investigation, chronic non-paroxysmal cases are diagnosed more frequently.

According to MacKeith (1944) a considerable variety of conditions

hypopituitarism have low blood pressures but Perera (1952) found several examples of the co-existence of hypopituitarism and hypertension. Neither acromegaly nor giantism are regularly associated with hypertension but the pituitary form of Cushing's syndrome is likely to be associated with some blood pressure elevation and pituitary obesity may be associated with somewhat over-average blood pressures.

## The Adrenal Medulla — Phaeochromocytoma

In 1886, nine years before Oliver and Schäfer discovered the pressor action of the adrenal medullary substance, Frankel gave a vivid description of the symptoms of phaeochromocytoma in a girl of 18 years, who was shown at autopsy to have suprarenal tumours He noted the great tachycardia and paroxysmal rise of blood pressure which he attributed to effort associated with vomiting which occurred in the attacks. By mischance he provoked a very severe attack by an injection of pilocarpine. Labbé, Tinel and Doumer( 1922) were the first to attribute the symptoms of phaeochromocytoma to the release of adrenaline, and early reports of successful excision were made by Mayo (1927) and Shipley (1929). While most phaeochromocytomas are benign tumours of the suprarenal medulla, such tumours may arise from chromaffin tissue in other parts of the body. The condition is sometimes familial [63, 286]. Occasionally malignant phaeochromocytomas are encountered. Adrenaline and noradrenaline are secreted by benign and sometimes by malignant tumours. Symptomless phaeochromocytomas were found in 3 out of 15,984 consecutive autopsies by Minno et al. (1954).

*Clinical manifestations of phaeochromocytoma.* — Walton (1950) divided phaeochromocytomas into five categories namely, those exhibiting: (1) paroxysmal hypertension, (2) persistent hypertension, (3) *malignancy,* (4) *Addison's disease due to compression* of the suprarenal cortex and (5) an asymptomatic course. In addition there are: (6) phaeochromocytomas in which the main clinical manifestations *consist in peculiar visceral sensations* without much hypertension. The following are frequent clinical manifestations: (1) paroxysmal or continuous elevation of the blood pressure, (2) increased cardiac output, (3) vasomotor phenomena, (4) excessive sweating, (5) fasting blood sugar of 120 mg. per 100 ml. or more, (6) glycosuria, (7) basal metabolic rate of + 20 per cent or more, (8) postural tachycardia, (9) elevated temperature, (10) decreased renal blood flow, (11) albuminuria.

It is generally thought that the nerve endings of the sympathetic supply to sweat glands are cholinergic and the occurrence of sweating during paroxysmal attacks requires some explanation. Smithwick et al. (1950) has explained the sweating in phaeochromocytoma as being due to stimulation of the parasympathetic centres in an effort to

maintain homeostasis, but Haimovici (1948) has suggested that the sweat glands in man have an adrenergic supply.

Advanced retinal changes may occur sometimes. Gutman (1947) described a case of phaeochromocytoma causing malignant hypertension, papilloedema and retinal exudates, and leading to uraemia and death. Spalding (1947) and Rodin (1945) described phaeochromocytomas with grade 3 retinal changes which cleared after successful operation; and Richardson et al. (1955) and Sowry (1956) described reversal of grade 4 retinal changes.

Paroxysmal attacks of hypertension may occur spontaneously as the result of emotion or if the phaeochromocytoma is palpated or deliberately massaged or handled at an operation. Attacks are also induced by diagnostic procedures which will be mentioned later. It has been recognized for some time, however, that not all patients with phaeochromocytoma exhibit paroxysmal hypertension and the disease may be assumed to be essential hypertension until special investigation, operation or autopsy has indicated its true nature [28, 142, 184, 213, 281, 334, 353]. Green (1946) was impressed by the frequency with which patients with phaeochromocytoma developed a chronic persistent [illegible]

[illegible] exhibited a malignant hypertension, 20 at times had albuminuria, 11 had decreased excretion of phenolsulphonphthalein and ? had [illegible]

to a[illegible]

to be[illegible] that this form of hypertension may lead on to secondary manifestations.

Green (1946) concluded from his study of the literature that, even in the chronic stage, the removal of a tumour causes a fall in the resting blood pressure to normal levels in almost every case. He thinks, therefore, that even the chronic non-paroxysmal hypertension is still mediated by a humoral mechanism, and that there is [illegible] suggest the d[illegible]

throu[illegible]

chan[illegible] sclerosis. Goldenberg et al. (1950), however, postulate the development of a self-perpetuating mechanism as a late result of phaeochromocytoma on the basis of a degree of persistence of the hypertension following the operation.

Smithwick et al. (1950) described a series of [illegible] phaeochromocyto[illegible]

d[illegible]

p[illegible]

b[illegible]

o[illegible] cases are diagnosed [illegible] investigation, chronic non-par- [illegible] more frequently.

According to MacKeith (1944) a considerable variety of conditions

may be confused with phaeochromocytoma, notably: essential hypertension, eclampsia, angina, hyperthyroidism, peptic ulcer, chronic nephritis, periarteritis nodosa, migraine, cardiac neurosis and anxiety states.

*Investigations in suspected phaeochromocytoma.* — As phaeochromocytomas may be malignant a search should be made for secondary deposits. X-ray examination may outline a tumour, especially if there is calcification, and unusual locations in the abdomen or thorax may be revealed. Tomograms may be of value and also x-ray pictures taken after perirenal injections of air. Air injection, however, carries a small risk of air embolism. Radiological techniques may not reveal tumours which are small in size or in unusual locations.

Excretion of Catecholamines: A most valuable indication of the presence of a phaeochromocytoma is an increase in the urinary excretion of catecholamines. Richter (1940) was the first to demonstrate the urinary excretion of adrenaline and of other sympathomimetic amines and the first account of their occurrence in normal human urine was made by Holtz et al. (1947). The diagnostic use was first described by Engel and von Euler (1950). Goldenberg and his collaborators (1954) have made extensive studies of the catechol content of the urine. Most of the catechols in human urine, they say, normally come from the sympathetic nerve endings and only a small amount from the adrenal medulla. The normal daily excretion is about 14 to 41 $\mu$g noradrenaline equivalent. In phaeochromocytomas the daily excretion of catechols in the urine may rise as high as 600 to 2700 $\mu$g. Goldenberg et al. (1954) describe a short procedure which consists in the adsorption of catecholamines from hydrolyzed urine on an aluminium hydroxide column. After this a photofluorometric estimate on the eluate may be used as a rough screening test. A longer and more specific method can be employed for confirmation.

Goldenberg et al. (1954) found that the urinary excretion of catecholamines in essential hypertension was, as an average, somewhat over the normal; but in patients with hypertension who had been subjected to a sympathectomy the urinary excretion fell below the average normal figure. Von Euler, Hellner and Purkhold (1954) also studied the excretion of noradrenaline in essential hypertension. They found that in 500 unselected cases, including 341 females and 159 males, the noradrenaline secretion in the urine was normal in 66.2 per cent of the patients, i.e., the amount excreted was less than 57.6 $\mu$g. in 24 hours and was increased in 16.4 per cent, that is above 86.4 $\mu$g. per 24 hours. They agree with Goldenberg that the increased secretion of noradrenaline observed in some cases of hypertension is probably derived from the adrenergic nerves, particularly from vasomotor nerves. This is consistent with the report of Von Euler, Franksson and Hellstrom (1954a, b), who find that there are comparatively small amounts of

noradrenaline in the suprarenals in health, and even after adrenalectomy the diminution of the amount excreted in the urine is not very great. Manger et al. (1954) and Pekkarinen and Pitkänen (1955) also found the urinary excretion of catecholamines was normal in most hypertensives other than patients with phaeochromocytoma. A useful screening test for phaeochromocytoma is provided by the bio-assay of untreated urine on the cat's blood pressure, as described by Moulton and Willoughby (1955).

Manger et al. (1954) also find an increase in the plasma catecholamine is present in patients with phaeochromocytoma, especially after pro-

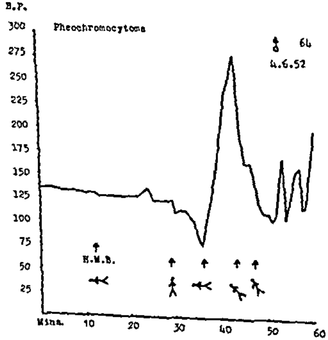



Fig VI 3

Provocation of a hypertensive attack in a patient with phaeochromocytoma, by blood pressure reduction induced by an injection of hexamethonium bromide.

vocative tests with histamine. In contrast, apart from phaeochromocytoma, the height of the blood pressure seems to be independent of the concentration of pressor amines in the plasma.

Hoobler et al (1951) found a d...

en...

val ...ically and as a research tool ...igation will prove

M

**Provocation of Hypertensive Episodes.** The following substances have been used to excite paroxysms of hypertension in patients with phaeochromocytoma; appropriate doses are given in brackets:

1. *Histamine acid phosphate (0.025 to 0.05 mg. of the base intravenously).*
2. Mecholyl (10 mg. subcutaneously).
3. Tetraethyl ammonium chloride (300 mg. intravenously within several seconds).
4. Hexamethonium bromide (15 mg. intravenously, the hypotensive action being assisted by tilting or by the sitting posture). An example of a hypertensive episode provoked by hexamethonium is seen in Fig. VI 3.

All of these tests may on occasion give false positive or occasionally false negative results. Evans et al. (1951) think that Mecholyl, in a 10 mg. dose subcutaneously, is the safest and simplest screening procedure. They believe that control patients vary in their reactivity to such tests, and for a positive result, to indicate phaeochromocytoma, they believe that the overshoot of the pressure should be greater than the response to the cold pressor test. These authors point out that the response to the test and the symptoms induced will depend upon the relative and absolute amounts of adrenaline and noradrenaline liberated Noradrenaline, compared with adrenaline, is less active in raising the blood sugar and has a smaller action on the heart, but it has a bigger action on the blood pressure Adrenolytic drugs have less effect upon the pressor action of noradrenaline than they have on the action of adrenaline. Evans et al. (1951) think that the blood pressure readings should be taken for at least half an hour after the use of a provocative agent as they have encountered several delayed reactions Calkins et al. (1951) consider that the histamine test is not always reliable and may produce false negatives and false positives.

Rises of blood pressure of over 100 mm Hg systolic and 50 mm. diastolic may occur on occasion with provocative tests. Consequently, there is some danger with provocative tests and it is well to have an antidote available. Where Mecholyl is used, 1/50th gr. of atropine should be in a sterile syringe ready for intravenous injection, to combat toxic reactions. Phentolamine (Regitine) may be of value in that it counteracts the action of liberated adrenaline and noradrenaline.

**Tests Depending on Adrenolytic Drugs.** The substance F933 has been used in the diagnosis of phaeochromocytoma. It antagonizes the pressor action of adrenaline and noradrenaline but is regarded by many authorities as an unsatisfactory diagnostic agent in phaeochromocytoma. Drill (1949) reported the occurrence of marked rises in the systolic blood pressure following the administration of F933

two patients with suspected phaeochromocytoma. Such rises of pres-
patients with essential hypertension in the absence of
(Regitine)

even of whom had phaeochromocytoma
Where hypertension was due to phaeochromocytoma
more than 35/25 mm., whereas
re were
Shaw
blocking
(1956) considers the use of Regitine
test, but false positive reactions are not infrequent in his experience.
*phaeochromocytomas.* — The surgical treatment
d by the fact that the tumours
of
nds [277], and sometimes tumours
ar
are multiple, sometimes bilateral [2403, 2406] and they
are sometimes familial [63, 69, 174, 181, 209, 286].

Philips (1940) and Maier (1949) described the occurrence of intra-thoracic phaeochromocytoma with hypertension. Chest x-rays are therefore desirable
Usually a
the costov
only two cases of intrathoracic phaeochromocytoma had then been
Some 12 per cent of
in the literature were
(1945) reported a case
and reviewed 16 others
the organs of Zuckerkandl. These organs are situated along the aorta and near to the origin of the inferior mesenteric artery. The tumours are of a chromaffin type and consist of a collection of phaeochrome cells. West et al. (1953) state that, in histological structure, phaeochromocytomas of the organ of Zuckerkandl resemble other chromaffin tissue and do not differ from the phaeochromocytomas of the adrenal medulla. During foetal life, the organs of Zuckerkandl contain noradrenaline and a little adrenaline. After birth fibrosis begins and pharmacological activity decreases, and by the third year of life only a little pressor amine is discoverable.

Malignant phaeochromocytomas have been described by several authors and it is apparent that many such cases are unaccompanied by hypertension. McGavack et al. (1942) reviewed the literature and found 8 cases with no hypertension and Bauer and Belt (1947) also thought that the malignant tumours did not cause hypertension. Apparently there are exceptions, for Cross *et al.* (1951) described a malignant phaeochromocytoma with metastases, and hypertension was present until the primary growth was removed. Calkins et al. (1951) also described a case with malignant phaeochromocytoma and widespread

metastases. In this case, however, after removal of the primary tumour, the administration of histamine still gave rise to paroxysmal attacks. Davis et al. (1955) also described a case with functioning metastases.

Eisenberg and Wallerstein (1932) referred to the occurrence simultaneously of phaeochromocytomas and other types of tumour, for example, neurofibromata. They discovered nine instances of this combination in the literature.

On occasion, syndromes which resemble the classical picture of phaeochromocytoma closely may be encountered in patients who fail to exhibit tumours even on extensive exploration [10, 112]; hence, it is of considerable practical importance to obtain confirmatory evidence by means of ancillary investigations.

*Surgical treatment.* — Following surgical removal it is commonly found that the blood pressure falls rapidly soon after tying the veins which convey secretion from the tumour into the circulation. It is desirable to administer noradrenaline, which is preferable to adrenaline, *by continuous slow injection. It must be remembered that* patients who have had a phaeochromocytoma are much less sensitive than the average to adrenaline and noradrenaline. Consequently, the doses which may need to be administered are considerable. Even with meticulous post-operative care, the fatalities have been numerous, and the original literature should be consulted by those contemplating such procedures

A splendid series of 25 patients treated surgically, with no deaths, has been reported by Kvale et al. (1954). This suggests that it is possible for the removal of a phaeochromocytoma to be made comparatively safe.

## The Adrenal Cortex

*Adrenal adenoma, with and without Cushing's syndrome.* — Some of *the early observations relating adrenal cortex tumours to hypertension* were reviewed by Oppenheimer and Fishberg (1924) and a further review of the subject was published in 1935 by Bauer. A study of the relation of the adrenal cortex to hypertension was made by Russi, Blumenthal and Gray (1945), who studied 9,000 autopsies and in 131 of these discovered adenomata of the adrenal cortex. These adenomata were, in general, much smaller than those encountered in Cushing's syndrome. The incidence was 2 per cent in the females and 1 2 per cent in the males, and most of the adenomata occurred in patients over the age of 40.

Russi and co-workers (1945) related these findings to the clinical data. Taking a blood pressure of 140/90 mm. Hg or over as evidence of hypertension, they found over 100 of the patients with adrenal-*cortical adenomata could be considered hypertensive* as compared with 54.9 per cent of a clinical group collected by Master, Marks and Dack

[illegible]

cortical adenomata as it was in the control group; and when the figures were adjusted for age, hypertension was three to four times as common in each age group. Of the 1,254 autopsies on hypertensives, 7.4 per cent had tumours, whereas in the whole series of autopsies the incidence was 1.45 per cent. The incidence of diabetes in the whole series was approximately 3 per cent, but among patients with cortical adenomata 16 per cent had diabetes, and all but two of the diabetics also had hypertension. Schroeder (1953) concludes, on the evidence provided by Russi et al., that most patients with adrenal-cortical adenomata have hypertension. It would be desirable to know more of the relationship between these tumours and the occurrence of more substantial degrees of hypertension.

Commons and Callaway (1948), however, studied 9,866 consecutive autopsies. They found that adenomas occurred particularly in patients over 40 years, and discovered no significant difference in the incidence of hypertensive cardiovascular disease or cardiac enlargement in patients with and without adenomas of the adrenal gland. Fisher and Hewer (1947) thought that the amount of adrenal cortical lipoid was increased in essential and in renal hypertension.

Smithwick (1948) states that the incidence of cortical adenomata in a large number of hypertensive individuals is 4 per cent. Schroeder (1953) refers to a study of 4,000 autopsies by Davis and Schroeder. They picked out the cases with adenomata, focal hyperplasia and diffuse hyperplasia of the adrenal cortex, and they found that morphological evidence of some overactivity of the adrenal cortex was present in 1.75 per cent of the autopsy cases, which figure is comparable with the 1.45 per cent of Russi et al. Among the patients with evidence of cortical overactivity, they found 96 per cent with cardiac hypertrophy [illegible] found 75 per c[illegible] 47 per cent. S[illegible] weights over 350 gm. in the male and 300 gm. in the female, or 50 gm. above the expected heart weight, as evidence of hypertrophy. But only 30 per cent died from the effects of hypertension, in which he includes coronary occlusions, cerebral accidents and heart failure. He thinks that [illegible]

was present in 38 per c[illegible]

He defines his "endoc[illegible]

of a disturbance wh[illegible]

He sets out some of [illegible]

age when first exam[illegible] average age with the most

rapid gain in body weight, 30 years; the average maximum weight was 215 lb. There were stria in 77 per cent, acne in 21 per cent, carbohydrate disturbance in 25 per cent and easy bruising in 60 per cent. A majority of the patients said that they liked plenty of salt in their food, only four said that they did not like salt. He thinks there is a definite syndrome which is important because (1) the hypertension is sensitive to the restriction of salt in the diet; (2) that grade 4 fundi are less serious in their significance; (3) that the patients have difficulty in losing weight; (4) that the use of hyphex is relatively less efficient.

Perera (1952) thinks that hypertensives handle the addition of salt and its restriction in a manner which differs somewhat from the normal, and that in some way the adrenal gland is concerned with this difference. "The addition and subtraction of dietary salt has a small but consistent effect on the blood pressure of uncomplicated hypertensives but is without effect in normotensives. In a hypertensive with adrenal cortical insufficiency excessive salt intake does not influence the blood pressure, unless small daily injections of desoxycorticosterone are administered."

Eisenberg et al. (1950) studied the sodium concentration in sweat as an index of the adrenal cortical function in essential hypertension. They found that the sweat sodium concentration in patients with mild or severe hypertension is not significantly different from the normal, and therefore consider it unlikely that ordinary essential hypertensive patients have any considerable increase in the adrenal cortical steroids which influence electrolytes; for, when there is an excess of these substances, the sodium content of the sweat is decreased. Tobian (1949) made a study of corticosteroid excretion in the urine by a modified Loewenstein method. He found that most patients with essential hypertension showed a normal corticosteroid excretion. Davis and Clark (1950) also studied the salt concentration in sweat. They distinguished a group of hypertensive patients with decreased salt concentration which they attributed to excessive action of the adrenal cortex hormones. This group of patients, they think, should not be included in the category of essential hypertension and may coincide to a large degree with the group described by Schroeder as the "endocrine hypertensive syndrome".

Our own experience with this particular group is limited to clinical observation but, among severe hypertensives, we do not seem to see many patients of this type. The clinical manifestations of Cushing's syndrome are not seen in the average patient with essential hypertension and it seems unlikely that the cortisone-like compound F can *be held responsible for the blood pressure elevation.* The alternative possibility, namely, that an excess of desoxycorticosterone-like hormone is present also seems unlikely and it is not certain that the adrenal cortex makes this substance. Indeed, it now seems that adrenal control

over sodium metabolism is mainly due to aldosterone which is approximately twenty times as active as D.C.A."

The fact that there is usually a degree of hypertension in Cushing's syndrome and hypotension in Addison's disease indicates that the adrenal cortex may cause changes of the blood pressure level. There are, however,[67, 201, 228] exceptional instances of the occurrence of hypertension in Addison's disease.

"Many patients with Cushing's syndrome, who exhibit obvious endocrine manifestations, have comparatively small increases of blood pressure. Alterations in the secretion of adrenal cortical hormones do not appear to play a pre-eminent pathogenetic role in the average case of essential hypertension, but the possibility that such hormones may exercise a minor role in some patients and a more substantial part in a few patients requires further study.

It is of interest that when hyperfunction of the adrenal cortex is initiated in intrauterine life, the resulting pseudohermaphrodism is seldom associated with hypertension[119].

*Adrenal cortex carcinoma* may cause endocrine manifestations and hypertension. Davies (1952) described Cushing's syndrome in a child of 2½ with a blood pressure rise to 200/140. The condition was due to an adrenal cortex carcinoma arising almost certainly in aberrant

... carbohydrate metabolism in a diabetic direction. Her blood pressure had risen to 150/100. A female patient in the care of my colleague, Professor Caughey, had a large carcinoma of the adrenal cortex with hyper...

x-ray

return ... metastases, but without recurrence of the symptoms of Cushing's syndrome.

*The Achard-Thiers subtype of Cushing's syndrome* is Cushing's syndrome with diabetes which ...

hypertension. Sh...

18

of

the ... ...ing most of the features of the Achard-Thiers syndrome, together with gynaecomastia. "The condition was due to bilateral hyperplasia of the adrenal cortex and a large adrenal cortex adenoma." The blood pressure was only 180/110 and this might have been coincidental.

*Aldosteronism.* — Using a paper chromatography ... tion on adrenal ...

a strong

now kn...

...enty-five times as active in

rapid gain in body weight, 30 years; the average maximum weight was 215 lb. There were stria in 77 per cent, acne in 21 per cent, carbohydrate disturbance in 25 per cent and easy bruising in 60 per cent. A majority of the patients said that they liked plenty of salt in their food, only four said that they did not like salt. He thinks there is a definite syndrome which is important because (1) the hypertension is sensitive to the restriction of salt in the diet; (2) that grade 4 fundi are less serious in their significance; (3) that the patients have difficulty in losing weight; (4) that the use of hyphex is relatively less efficient.

Perera (1952) thinks that hypertensives handle the addition of salt and its restriction in a manner which differs somewhat from the normal, and that in some way the adrenal gland is concerned with this difference. 'The addition and subtraction of dietary salt has a small but consistent effect on the blood pressure of uncomplicated hypertensives but is without effect in normotensives. In a hypertensive with adrenal cortical insufficiency excessive salt intake does not influence the blood pressure, unless small daily injections of desoxycorticosterone are administered.'

Eisenberg et al. (1950) studied the sodium concentration in sweat as an index of the adrenal cortical function in essential hypertension. They found that the sweat sodium concentration in patients with mild or severe hypertension is not significantly different from the normal, and therefore consider it unlikely that ordinary essential hypertensive patients have any considerable increase in the adrenal cortical steroids which influence electrolytes; for, when there is an excess of these substances, the sodium content of the sweat is decreased. Tobian (1949) made a study of corticosteroid excretion in the urine by a modified Loewenstein method. He found that most patients with essential hypertension showed a normal corticosteroid excretion. Davis and Clark (1950) also studied the salt concentration in sweat. They distinguished a group of hypertensive patients with decreased salt concentration which they attributed to excessive action of the adrenal cortex hormones. This group of patients, they think, should not be included in the category of essential hypertension and may coincide to a large degree with the group described by Schroeder as the "endocrine hypertensive syndrome".

Our own experience with this particular group is limited to clinical observation but, among severe hypertensives, we do not seem to see many patients of this type. The clinical manifestations of Cushing's syndrome are not seen in the average patient with essential hypertension and it seems unlikely that the cortisone-like compound F can be held responsible for the blood pressure elevation. The alternative possibility, namely, that an excess of desoxycorticosterone-like hormone is present also seems unlikely and it is not certain that the adrenal cortex makes this substance. Indeed, it now seems that adrenal control

over sodium metabolism is mainly due to aldosterone which is approximately twenty times as active as D C.A."

The fact that there is usually a degree of hypertension in Cushing's syndrome and hypotension in Addison's disease indicates that the adrenal cortex may cause changes of the blood pressure level. There are, however,[67, 207, 228] exceptional instances of the occurrence of hypertension in Addison's disease.

"Many patients with Cushing's syndrome, who exhibit obvious endocrine manifestations, have comparatively small increases of blood pressure. Alterations in the secretion of adrenal cortical hormones do not appear to play a pre-eminent pathogenetic role in the average case of essential hypertension, but the possibility that such hormones may exercise a minor role in some patients and a more substantial part in a few patients requires further study.

It is of interest that when hyperfunction of the adrenal cortex is initiated in intrauterine life, the resulting pseudohermaphrodism is seldom associated with hypertension[119]

*Adrenal cortex carcinoma* may cause endocrine manifestations and hypertension Davies (1952) described Cushing's syndrome in a child of 2½ with a blood pressure rise to 200/140 The condition was due to an adrenal cortex carcinoma arising almost certainly in aberrant [illegible]

[illegible] to 100/100. A female patient in the care of my colleague, Professor Caughey, had a large carcinoma of the adrenal cortex with hypertension and masculinization (Fig. VI 4a, b). On deep x-ray treatment the patient's appearance, as well as her blood pressure, returned to normal. She died with metastases, but without recurrence of [illegible]

syr[illegible] *syndrome* is Cushing's [illegible] expected, may be associated with hypertension. Shepardson and Shapiro (1939) refer to a collection of 18 cases from the [illegible]

[illegible] most of the features of the Achard-Thiers syndrome, together with gynaecomastia. The condition was due to bilateral hyperplasia of the adrenal cortex and a large adrenal cortex adenoma. The blood pressure was only 180/110 and this might have been coincidental.

*Aldosteronism.* — Using a paper chromatography method of separation on adrenal [illegible] a stron[illegible] Bush (1952) found now k[illegible] The active fraction, [illegible], is at least twenty-five times as active in

controlling sodium and potassium excretion by the kidney as desoxycorticosterone, and according to Mach et al. (1954) and Gross et al. (1954) aldosterone also differs from desoxycorticosterone in not readily producing hypertension experimentally in rats.

It seems clear that an aldosterone-like substance is excreted in the urine in response to a number of situations which require adjustment of the blood circulation. Farrell et al. (1956) found that when dogs were bled there was an increase in the discharge of aldosterone into the

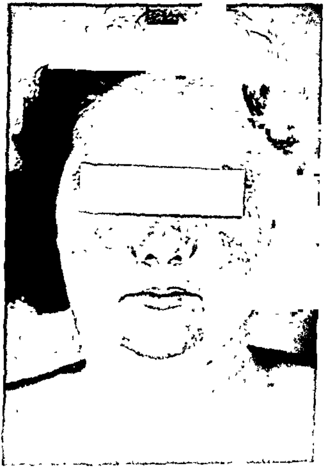


Fig VI 4a

Masculinization, skin striae and hypertension in a patient with Cushing's syndrome due to carcinoma of the adrenal cortex

adrenal vein blood and that the aldosterone response was prevented by the infusion of dextran in saline. Llaurado (1955) found an increased urinary excretion of aldosterone immediately after surgical operations.

Luetscher and Johnson (1954) found a sodium retaining principle (presumably aldosterone) in the urine of heart failure patients and in patients with oedematous nephritis; and Luetscher and Axelrad (1955)

found that restriction of sodium intake in two healthy men was followed by increased aldosterone output.

Genest et al. (1956), finding that hypertensive patients secrete

... however,

use for



Fig VI 4b

Masculinization, skin striae and hypertension in a patient with Cushing's syndrome due to carcinoma of the adrenal cortex

essential hypertension Although hypertens...

... have

potassium-losing nephritis with periodic paralysis, has since been shown to be an example of primary aldosteronism due to an adrenal tumour. Her blood pressure was 180/110.

Dr. Posborg Petersen of Aarhus, Denmark, kindly supplied me with the case history of a 13 year old girl who was admitted to hospital after a 4 months' history of increasing muscular weakness and generalized convulsions. She developed hypertension, proteinuria, polyuria and papilloedema. Persistent hypokalaemia and increased aldosterone excretion (36 $\mu$g per 24 hours) was demonstrated. The left adrenal which was grossly and histologically normal was removed with electrolyte improvement. Hypertension persisted and then was treated for a time with Ansolysen, but stayed down at a level of 150/100 when this was discontinued.

*Barnes and Quilligan (1956) have reported a marked increase in the* sodium retaining activity of the urinary corticoids in eclamptogenic toxaemia.

Demonstrable hyperaldosteronism is a comparatively rare condition but there is good evidence that it may be associated with blood pressure elevation which may be relieved if an aldosterone secreting tumour is removed from an adrenal gland. Such cases, however, are readily distinguished clinically from essential hypertension though they have sometimes been regarded in the past as examples of potassium-losing nephritis. According to Conn (1955) cortical tumours are not *found in all cases of aldosteronism.*

## The Thyroid Gland

It is usually supposed that the elevation of the systolic blood pressure *in cases of thyrotoxicosis is an expression of the increase* in cardiac output. The diastolic pressure is seldom raised concurrently to any important extent. As Fishberg (1954) points out, patients with a degree of essential hypertension may develop more substantial blood pressure elevation if the cardiac output is increased by an excess of thyroid hormone. Recently Braun-Menendez (1954) found that the height of the blood pressure in the Goldblatt type of experimental *hypertension was increased by the administration of* thyroid hormone and decreased by thyroidectomy. It may be that an excess of thyroid hormone can occasionally work in this way in human hypertension In clinical myxoedema the blood pressure may be either elevated or normal Aside from thyrotoxicosis, there may be a moderate increase of basal metabolic rate in patients with substantial hypertension [245, 255]

## The Parathyroid Gland

The activities of the parathyroid gland may be indirectly related to hypertension. In primary hyperparathyroidism deposits of calcium in the kidneys may lead to impairment of renal function with fibrosis and *blood pressure elevation.*

In cases of nephritis there is often a moderate degree of hypertrophy of the parathyroid gland which is probably due to failure to excrete phosphate adequately. The injection of phosphate experimentally may cause parathyroid hyperplasia. The complex changes which result appear to be the cause of "renal rickets" in children and of decrease of blood calcium with, on occasion, osteoporosis in cases of advanced renal disease in adults. The changes in calcium metabolism are of a smaller degree in adults than in children. Excretion of fixed base, including calcium, due to the inability of the damaged kidneys to form a highly acid urine is an additional factor concerned in loss of calcium from bones.

### The Menopause

No dramatic blood pressure change appears to have been reported in relation to the menstrual cycle There is a widespread impression that the menopause is concerned in the development or first appearance of hypertension in women The graphs relating blood pressure to age do not, however, show any special increase in mean blood pressure levels at this time of life. Taylor, Corcoran and Page (1947) hold the view that any relation between blood pressure and the menopause is purely coincidental They find, in support of this view, that ovariectomy at an early age does not induce hypertension. [illegible] (1953) on the other hand thinks
at the menopause and it has [illegible]
sometimes drops after the menopause.

Gram (1930) reported the frequent association of the menopause with obesity, tender subcutaneous infiltrations, arthritis of the knee joint and arterial hypertension, and cites many case histories. The important question is whether the relationship is coincidental or whether, as he thinks, this represents a special form of hypertension.

There is very little doubt that hypertension in females is on the increase about the time of [illegible]
menopause as such has mu[illegible]
recollected that many wom[illegible]
a variety of discomforts. In consequence the discovery of an elevated blood pressure may occur more frequently at this time of life.

## HYPERTENSION ASSOCIATED WITH PREGNANCY

The hypertension associated with pregnancy may be described under four headings -

1. Pregnancy toxaemia, including toxaemia with convulsions (eclampsia)
2. Post-pregnancy toxaemia [illegible]
3. E[illegible]
4. P[illegible]

These disorders are not entirely independent, for there is evidence that essential hypertension predisposes to the development of toxaemia, which latter may lead to further rise of the blood pressure during pregnancy, and after parturition the level of the blood pressure may not fall to the original level.

In patients who are known to have had a normal blood pressure before and in the early stages of pregnancy and who, therefore, may be considered as free from essential hypertension, the pregnancy toxaemia may leave behind a hypertension which is indistinguishable from essential hypertension, except that the clinical history may reveal that it began with pregnancy toxaemia. In addition to these, pyelonephritis and glomerulonephritis may precede pregnancy or occur during its course.

## Pregnancy Toxaemia (including Eclampsia)

*Clinical features.* — In almost all instances, pregnancy toxaemia begins in the last four months of pregnancy. When it is of severe degree the diagnosis is made easily but, when there is a mild pregnancy toxaemia, it may resemble a coincidental essential hypertension, or a degree of sodium and water retention which, while not definitely abnormal, is greater than that ordinarily encountered in pregnancy. When elevation of the blood pressure is associated with oedema which extends to the face or hands, or if there is more than a trace of protein in the urine, the diagnosis is likely to be pregnancy toxaemia.

In severe cases the blood pressure may be over 170/110, oedema may be considerable and proteinuria may amount to 5 gm. or more per 24 hours. The chance of foetal death is increased to 25 per cent or more and the maternal mortality may be in the region of 1.7 per cent, though it has been reduced well below this level in some hospitals.

**Convulsions.** In some of the most severe cases of pregnancy toxaemia convulsions occur, and the condition is then called eclampsia. While proof is lacking, it seems likely that the only difference between the cases called pregnancy toxaemia and those described as eclampsia consists in the presence of convulsions, which are more likely to occur when toxaemia is severe. It seems likely, from electroencephalographic evidence[283] that the toxaemia patients who are most likely to develop convulsions are those with primary cerebral dysrhythmias, the threshold for convulsive seizures being further lowered by the toxaemia.

[illegible]

a f [illegible]

few instances of convulsions among approximately 1000 cases [illegible] sential hypertension without renal damage; though temporary losses of consciousness and pareses have occurred frequently in untreated patients. The blood pressures of eclamptic patients are often at a level

which would cause no immediate concern in a non-pregnant patient, but the impression is that, apart from pregnancy, convulsions are much more frequent when in addition to hypertension, sodium retention or renal damage is present.

**Retinal Changes.** Spasm of retinal arteries appears to be one of the earliest retinal changes in pregnancy toxaemia [130, 137, 345]. Normally the ratio of artery to vein diameters is 2 to 3 and in the presence of spasm this may fall as low as 1 to 4 or even 1 to 6. In more severe conditions retinal oedema, haemorrhages and soft exudate may appear. We have often noted in our clinic that the retinopathy appears with much lower levels of the blood pressure than are required to induce similar changes in essential hypertension. Severe retinal changes may be present with blood pressures under 180/120.

[illegible] retinopathy is present the [illegible] permanent hypertension is increased [illegible] [illegible]ently described a wet glistening appearance of the fundus as an early manifestation in toxaemia. This may be difficult to distinguish from the normal retinal sheen of young people.

**Albuminuria and Organized Deposits.** When a hypertension in the course of pregnancy is associated with the presence of much proteinuria it is unlikely that the hypertension is present coincidentally. The urine may also contain red cells and various forms of casts

**Oedema** Fluid retention occurs in normal pregnancies and moderate oedema of the legs is not an indication of toxaemia. Dieckmann (1952) considers oedema of the face and hands as abnormal but Dexter and Weiss (1941) state that some oedema of the face or hands may be present in 64 per cent of normal pregnancies. Although there may be considerable fluid retention without the subsequent development of pregnancy toxaemia, the observation of an excessive gain in weight (over 600 gm. per week) or an unusual degree of oedema, is a warning that pregnancy toxaemia may be developing.

No sufficient explanation for the fluid retention has been found, but an increase in the secretion of steroid hormones in the course of pregnancy [324] seems to be the most favoured explanation. The kidney function is ordinarily normal, but in severe pregnancy toxaemia an oliguria, or even suppression of urine, may occur [93]. In most instances the concentrating power of the kidneys is within normal limits and the blood urea is normal. The low plasma volume in pregnancy toxaemia [35, 93, 125] is difficult to reconcile with increased secretion of corticoids [336] in the last trimester.

**Hypertension** This is one of the most frequent manifestations of pregnancy toxaemia and the blood pressure level is often higher in

the more severe cases, particularly in those with eclamptic convulsions

Normally in pregnancy there is a drop of 5 or 10 mm. in the systolic pressure between the eighth and thirty-second week and a return to the original non-pregnant level as pregnancy advances. Unless the blood pressure was elevated beforehand, a level of 140/90 in the last four months of pregnancy is to be regarded as favouring a diagnosis of early toxaemia. In many of these patients the blood pressure level remains high after parturition, or falls only to rise again some months " or years afterwards. *Furthermore, many of the patients who develop* pregnancy toxaemia have a family history of hypertension [55, 93]. Hence, the suggestion has been advanced that the pregnancy toxaemia has precipitated an essential hypertension which, in any case, would have developed later in life had there been no toxaemia."

"In support of the contention that pregnancy toxaemia does not increase the incidence of hypertension, Isenhour et al. (1942) point out that statistics reveal no difference in the incidence of hypertension between single and married women. But the validity of the statistical evidence has been challenged [132]. It is possible also that increased emotional tension or some other cause operating especially in single women may balance the effects of pregnancy toxaemia on female statistics It seems very likely that patients who are hereditarily predisposed to hypertension may respond more readily to the stimuli provided by pregnancy toxaemia and that blood pressure increases so induced are more likely to be perpetuated.'

It is difficult to estimate the influence of antecedent hypertension. Teel and Reid (1937) found in a follow-up study that 27.5 per cent of patients with eclampsia developed hypertension, but when they selected 29 post-eclamptics who were known to have been healthy prior to the eclampsia, none had residual albuminuria or evidence of impaired renal function, and only three (10 3 per cent) showed hypertension. There are those who take the extreme view that women who were normal before a pregnancy toxaemia, do not subsequently have a higher incidence of hypertension than would be expected in women of the same age group, apart from pregnancy. Peckham (1941), however, found a much greater expectation of permanent hypertension in patients who had had many weeks of hypertension from pregnancy toxaemia. The tendency to subsequent hypertension was noted in *primipara* who had carried a child for over twelve weeks after the start of toxaemic manifestations and in multipara who had carried the child for more than six weeks He advised early termination of the pregnancies.

The blood pressure level in pregnancy toxaemia seems to be influenced by the salt intake. Harding and Van Wyck (1926) and Dieckmann (1952) found that the administration of additional salt increased the hypertension and albuminuria as well as the oedema.

... the blood pressure. ... on the blood pressure ... aneously was trivial in normal pregnant women and those with essential hypertension, a systolic blood pressure rise of about 20 mm. Hg was usually observed in patients with pregnancy toxaemia. Occasionally the systolic blood pressure increase exceeded 60 mm. Hg.

*Pathology.* — The changes observed at autopsy may not explain why death has occurred. Perhaps the most characteristic of the findings in patients dying of pregnancy toxaemia is the thickening of the walls of the glomerular loops [17, 81, 113]. These changes, however, do not always give rise to gross alterations in the microscopical appearances and according to Zimmerman and Peters (1937) such changes may be absent. Sometimes the glomerular changes seem enough to account for the rise of blood pressure. Very rarely the kidneys exhibit bilateral cortical necrosis. There is no proof that the manifestations of pregnancy toxaemia are of renal origin and, indeed, Sheehan (1950) has suggested the possibility that the renal changes are secondary to spasm of the afferent glomerular arterioles.

In patients dying from eclampsia, pulmonary oedema and oedema of the brain [361] are often encountered and punctiform haemorrhages of the brain may be present also. When coma supervenes in severe pregnancy toxaemia the cause is usually found to be cerebral haemorrhage but shorter periods of coma may be a sequel of convulsive episodes.

Changes in the liver usually occur later than those in the kidneys. There may be haemorrhagic necroses in the periportal areas. Degenerations and infarctions of the placenta are encountered and Young (1942) regards the pregnancy toxaemia as due to the placental ...
c ...
t ...
The changes are thought by some authors [25, 323] to progress more rapidly in pregnancy toxaemia than in health.

When death occurs in pregnancy toxaemia it is usually due either to eclampsia or to pulmonary oedema brought about by left ventricular failure and sodium retention.

*Pathogenesis.* — While the pathogenesis of pregnancy toxaemia remains obscure, there has been an accumulation of ...
terestin...
of the p...
with ab...
conside... of pregnancy toxaemia. It is consistent with its occurrence in the later months of pregnancy and with its prompt relief when pregnancy ends. The early occurrence of endarteritis in placental blood vessels and the presence of infarcts

directed attention to the probability of a decrease in placental blood flow. Bastiaanse and Mastboom in 1949 reported that uterine ischaemia, induced by partial occlusion of the uterine arteries, caused hypertension in the pregnant but not in the non-pregnant bitch.

An estimate of the placental blood flow in normotensive and hypertensive women and in pregnancy toxaemia has been made by Browne and Veall (1953). After discovering patients with anteriorly placed placentas, they injected $Na^{24}$ into the placental blood pool and then measured the rate of its disappearance. They found that in essential hypertension and in toxaemia the estimated placental blood flow was reduced to about one third of the normal 600 ml. min. Cox and Chalmers (1953) found the rate of transfer of $Na^{24}$ across the placenta from mother to foetus was reduced in pregnancy toxaemia. This observation is also consistent with a diminished placental blood flow in toxaemia. Furthermore, Clemetson and Churchman in 1953 found that the oxygen saturation of the blood in umbilical veins was equal in health and in pregnancy toxaemia, but the saturation in the umbilical artery was reduced from the normal of 31.5 to 16.1 per cent in pregnancy toxaemia.

It seems very likely that the foetus gets an inadequate blood supply in toxaemia. This may account for the clinical impression that babies born to toxaemic mothers are smaller.

There is no proof that the ischaemic placenta liberates pressor substances but the possibility is of great interest and derives some support from the occurrence of monoamine oxidase in the human placenta. The activity of this enzyme in the placenta is related to the oxygen tension [333] as it is also in the kidney. Hence the suggestion arises that the ischaemic placenta may fail to destroy pressor amines. It has been pointed out by Clemetson and Churchman (1953) that a primary mechanism dependent on placental ischaemia would explain the increase in toxaemia in twin pregnancies and the rapid fall in blood pressure when the foetus dies *in utero* with the placenta still attached, for then the placental blood supply is improved. They point out that in concealed accidental haemorrhage, where the detached part of the placenta is anoxic, the blood pressure may remain high after foetal death.

The occurrence of toxaemia in the last months of pregnancy may be explained in terms of the physiological tendency of the foetus to outgrow its blood supply in the latter part of pregnancy (Barcroft, 1946). It is possible, however, that some of the placental changes are the result rather than the cause of pregnancy toxaemia.

Of interest is the great variation in the incidence of pregnancy toxaemia in different parts of the world (Theobald, 1930). It would be valuable to know more about diet including calories, protein and salt intake, and the relation to the incidence of hypertension, more par-

ticularly in poor eastern communities where the incidence of toxaemia is often low. According to Bastiaanse (1954) the incidence of eclampsia at the obstetrical clinic of the University of Amsterdam showed a marked decrease during the war years, especially in the famine winter. It is possible that undernutrition, with diminution in the size of the foetus, may be the explanation.

It is apparent that the incidence of eclampsia can be reduced greatly and the maternal and foetal losses from toxaemia diminished by meticulous ante-natal care; but the manner in which the ante-natal procedures which appear to have been responsible for improvement induce their effects is only partly explained.

Dawson (1953) lays emphasis on close ante-natal supervision, introduction of therapeutic measures at the first suspicion of toxaemia, including salt deprivation, and early admission to hospital with the object of securing physical and mental rest. From 1947 to 1950 Dawson's incidence of eclampsia had dropped to one out of 3012 "booked" cases and there were no maternal deaths. Hamlin (1952, 1953) of the Crown Street Hospital, Sydney, adopts measures similar to those used by Dawson in New Zealand, and lays emphasis also on increase of protein and decrease of carbohydrate in the diet. Since a campaign against eclampsia was instituted in the Crown Street hospital their incidence of eclampsia dropped from 100 in 37,000 "booked" cases to a final level of 1 in 7,000 cases.

Related in some measure to hypotheses concerned with placental ischaemia are those which attribute pregnancy toxaemia to endocrine changes. The review by Smith and Smith (1948) gives an excellent summary. They say: "*Certain aberrations from the normal in hormonal or hormonal-like findings and in placental morphology appear to be established in women with pre-eclampsia and eclampsia*: 1, excessive antidiuretic substance in urine and placenta; 2, melanophore-expanding principle in the blood and placenta; 3, a hypersensitivity to the injection of posterior pituitary secretions; 4, high titers of chorionic gonadotropin in a large percentage of cases; 5, decreased excretion of estrogens and pregnanediol ...

... probably secrete the steroid hormones. Of these established abnormalities, the last three are underway prior to clinical manifestations and occur normally at term". "The evidence at hand appears to establish premature senility of the placental syncytium and premature withdrawal of the placental steroid hormones as the final intermediary pathology. This disturbance, which occurs normally at ...

placenta or a decrease in blood supply to the placenta or both."

That the occurrence of endocrine stigmata such as abnormal hair distribution, overweight and acromegaloid features in women predisposed to pregnancy toxaemia was stressed by Vorzimer et al. (1937). An increased secretion of corticoids in the last months of pregnancy[336] is also highly significant, especially when considered in relation to the beneficial effect of salt restriction.

A major obstacle to the clinical investigation of pregnancy toxaemia is the difficulty in diagnosis. Not only is there a danger of diagnosing essential hypertension with physiological oedema as pregnancy toxaemia, but diagnoses of pregnancy toxaemia may not be made when this disorder is superimposed on essential hypertension. The occurrence of albuminuria is probably the least equivocal indication of the presence of pregnancy toxaemia. It is most unlikely to occur in essential hypertension at the blood pressure levels ordinarily met in pregnancy; glomerulonephritis is an infrequent explanation; and acute pyelonephritis is unlikely to be missed and is unlikely to raise the blood pressure.

## Essential Hypertension in Pregnancy

It is generally agreed that many patients formerly diagnosed as pregnancy toxaemia were patients with essential hypertension who had become pregnant. If antenatal studies reveal a raised blood pressure the condition is probably essential hypertension or, exceptionally, glomerulonephritis. Essential hypertension is more frequent in women over the age of 30, especially in those who have a family history of hypertension and who are either obese or of broad body build.

Such patients, however, may be seen for the first time late in pregnancy, and if at this time they have an overaverage gain of weight and some oedema, even though this is within normal limits, they may be diagnosed as pregnancy toxaemia incorrectly. The difficulty in diagnosis is increased by the fact that essential hypertension predisposes to the subsequent development of pregnancy toxaemia.

Essential hypertension increases the risk of foetal death from *abruptio placentae* and where the blood pressure is substantially elevated, the risk of foetal death is considerable. The blood pressure often increases further during the pregnancy and after the pregnancy the blood pressure may remain at a higher level. Where there is a family history of hypertension it seems that there is a greater risk during the pregnancy of substantial blood pressure elevation and of a residual hypertension following pregnancy

## Nephritis in Pregnancy

The occurrence of pregnancy in the course of glomerulonephritis is usually associated with a worsening of the nephritis and an increased

disposition to the development of toxaemia. It is not known whether this is due to pressure on the ureters, increase in the metabolic load, enhanced tendency to pregnancy toxaemia or to some other cause. The expectation of a living child is low. When hypertension, proteinuria, microscopic haematuria, urinary casts and impairments of renal function, occur early in pregnancy they are likely to be due to pre-existing renal damage, usually glomerulonephritis.

### Pyelonephritis and Pyelitis in Pregnancy

An acute pyelonephritis may occur, usually in the early months of pregnancy, or a previous pyelonephritis may be reactivated during pregnancy. The condition usually clears on appropriate treatment with antibiotics, sulphonamides and mandelic acid, but in a few instances a chronic pyelonephritis remains behind. Occasionally this is the cause of hypertension in later life. Crabtree (1940) has studied the late results of pyelonephritis of pregnancy. He found a high incidence of renal insufficiency but hypertension was present in only 8 out of 72 cases. In a group of 30 cases of severe pregnancy pyelonephritis, seen 10 to 18 years after the infection, 2 cases showed hypertension. The hypertension may have been coincidental.

## HYPERTENSION FROM ORGANIC NERVOUS DISORDERS

### Cerebral Lesions

Increase of intracranial tension from a cerebral tumour or purulent meningitis may cause an appreciable rise of blood pressure which is due apparently to brain stem compression. In animals, transverse sections through the mid-brain do not prevent the blood pressure rises from increased intracranial tension. It seems, therefore, that the effect of the compression is exercised at brain stem level.

Temporary blood pressure elevations of moderate degree are not infrequent after cerebral concussion and in some instances may be due to a rise in intracranial pressure. Raab (1949) described two patients with substantial blood pressure increases following head injury, which returned to normal on recovery. He reviews the literature.

Audier, Taddei and Rasmussen (1950) describe a case in which a patient whose blood pressure had been taken on many occasions previously developed a severe and lasting hypertension follo[illegible] head injury of m[illegible]

d[illegible]

o[illegible]

[illegible] described three cases of hypertension associated with bulbar paralysis. One of these was due to poliomyelitis and two of them to myelitis. The blood pressure rise lasted about two months. A very similar case of poliomyelitis was described by Nordmann and

Müller (1932) in a young man, with a rise of blood pressure to 209/140 mm. Hg on the day before death. Bolt et al. (1951) also described cases of considerable hypertension associated with paralysis of the tongue, palate and larynx, in bulbar poliomyelitis. They attributed the rise of blood pressure to asphyxia. Another explanation is the interruption of the buffer nerve pathways.

An excellent review of this subject has been published by Devic (1952) who has observed a number of cases himself. He discusses in detail the localization of the lesions which he believes to be in the medial portions of the reticular substance of the medulla. There is no doubt that medullary lesions may lead to considerable hypertension. One possibility is that the central connections of inhibitory mechanisms are damaged, such as those which arise from the carotid sinus and aortic arch or those which subserve the von Bezold reflex. Asphyxia alone does not seem to be an adequate explanation in all cases.

Grulee and Panos (1948) had 70 cases with bulbar poliomyelitis and encountered blood pressure elevation in 51; it persisted for an average of 3.4 days. In certain cases hypertension persisted for several days after the continuous administration of oxygen, suggesting that there was damage of cardiovascular centres.

Baker (1949) had 180 cases of bulbar poliomyelitis. They observed both rises and falls of blood pressure. In some instances there was a dusky flushed appearance and a pulse of 150 to 200 which they attributed to damage of the cardiovascular centres. Weinstein and Shelokov (1951), however, thought deficient oxygenation was the usual cause of hypertension in bulbar poliomyelitis but they recognized a less common variety, uninfluenced by the state of oxygenation.

Lachmund (1950) had 208 cases of poliomyelitis and encountered hypertension in 22, in all of which the medulla was involved. Loblich (1950) had 280 fatal cases of poliomyelitis and encountered hypertension in 10.

## Spinal Cord Lesions

Reference has been made already to reflex rises of blood pressure which occur in patients who have spinal cord lesions in the cervical or upper dorsal regions. These pressor reflexes are excited by distension of hollow viscera, more particularly the bladder and rectum[43, 147, 155, 268, 299, 331]. The paroxysmal rises of blood pressure can be prevented by ganglion blocking agents (Riskin et al , 1954). Bors and French (1952) in a series of 7 patients had successful results with bilateral posterior rhizotomy at the level of T9, 10 or 11 They consider, however, that posterior rhizotomy is only indicated when the paroxysmal hypertension becomes a threat to the life of the patient. The upper level of the posterior rhizotomy at the 9 or 10 thoracic segment was

chosen because afferent impulses reach the spinal cord at or below this region.

### Polyneuritis

"Lesions of the glossopharyngeal and vagus nerves have been reported by Lampen (1949) and by Kezdi (1954) to give rise to hypertension by interruption of the buffer nerve pathway.' Kezdi describes a case occurring in the course of a polyneuritis due to idiopathic porphyria. Waldenström (1937) considers that porphyria may act by stimulating the sympathetic nervous system. This might provide an alternative explanation. The characteristics of hypertension due to section of the sino-aortic nerves is that it is accompanied by permanent tachycardia and a high cardiac output, and that there is no response to carotid sinus pressure or to procaine block of the carotid sinus region

## RELATIONSHIP OF CERTAIN OTHER DISORDERS TO HYPERTENSION

### Coarctation of the Aorta

*Thoracic aorta* — Brachial hypertension in aortic coarctation is sometimes accompanied by a moderate increase of the blood pressure measured in the legs. It is generally thought that this may have arisen out of obstruction to the renal circulation. The prompt fall of brachial blood pressure which follows surgical treatment, and the occurrence of hypertension with coarctation of the abdominal aorta, indicate that renal ischaemia is not the sole cause of the hypertension. It is of interest, however, that while the blood pressure after surgical treatment falls promptly, it does not return to fully normal levels for at least several days.

It is important to diagnose the condition as most patients, if untreated, die before the age of 40 (Reifenstein et al., 1947), though occasional patients live to an advanced age An important cause of death is rupture of the aorta. Apart from this, death appears usually to be due to congestive heart failure or intracranial haemorrhage and secondary to the [illegible]
may occur Exc[illegible]
part of the body [illegible] after tonsillectomy and tooth extraction (Proudfit and Ernstene, 1949) One of our patients bled excessively from a head wound.

The presence of aortic coarctation should be suspected when hypertension occurs in young people. Palpation of the femoral arteries should be a routine in all patients with elevated blood pressure. X-ray examination may show notching of the under border of the ribs, a small aortic knob and undue clearness of the aortic window in the left

anterior oblique position. The ascending aorta may be dilated. Careful palpation of the back may reveal the pulsation of anastomotic vessels. Angiocardiography and tomography may yield useful information. Apparently the blood pressure should be measured in both arms for, exceptionally, coarctation may occur proximal to the left subclavian artery. In one of the two cases described by Burchell et al. (1950) the pressure in the right arm was given as 230/70 and in the left, 79/57. Dr. J. F. Goodwin of the British Postgraduate Medical School kindly provided me with details of a female patient aged 18 with aortic coarctation who exhibited papilloedema. The blood pressure in the arms was in the region of 190/120. There was no nitrogen retention. Following resection the arm blood pressure fell to 160/100 and the papilloedema cleared up.

*Abdominal aorta.* — This condition apparently led to renal hypertension in a patient described by Fisher and Corcoran (1952). The coarctation of the abdominal aorta interfered with the circulation of both kidneys. This was associated with a syndrome of malignant hypertension in a fourteen year old boy. Hypertension has occurred, however, with coarctation of the aorta just below the renal branches[18]. In this instance there was no reason to believe that substantial renal ischaemia existed. In the case described by Fisher and Corcoran there was actual obstruction to the openings of the renal arteries. There seems to be no doubt of the association between hypertension and coarctation of the abdominal aorta as well as between hypertension and coarctation of the thoracic aorta. The exact part played by alterations in the renal circulation is still undecided in both of these conditions.

### Non-cerebral Injuries

Grant and Reeve (1951) pointed out that injury unaccompanied by much blood loss might be associated with moderate blood pressure elevation. Howard et al. (1955a) made observations on war casualties in Korea. In 52 casualties arriving at hospital, as an average, 3 5 hours after wounding, the systolic blood pressures ranged from 140 to 240 and the diastolic from 80 to 140. Most men complained of more than average pain, but sleep induced by sedatives did not abolish the hypertension. The blood pressure elevations were abolished by pentothal, spinal anaesthesia, by hexamethonium and sometimes by Regitine. Howard et al thought that the condition was mediated by sympathetic nerves."The possibility that liberation of adrenal cortical hormones may play a part may have to be considered, despite the fall of blood pressure from hexamethonium. Howard et al. (1955b) found that combat stress and injury caused comparable increases in corticosteroid excretion."

## Periarteritis Nodosa

Periarteritis nodosa is a disorder with widespread lesions involving medium and small arteries, and sometimes veins and capillaries. The [illegible] to be due to hypersensitivity reactions to a wide [illegible] organic [illegible] also in [illegible] to be a severe forms of serum sickness. The [illegible] of an artery wall, associated with fibrinoid necrosis of part or all of an artery wall, associated with perivascular cellular infiltration, which may lead either to the formation of aneurysms or thrombosis. The fact that blood vessels almost anywhere in the body may be involved leads to a wide variety of clinical manifestations which are usually associated with pyrexia, unresponsive to antibiotics. The occurrence of limb pains, tender nodules, rapid pulse and renal manifestations or hypertension may direct attention to the possibility of periarteritis nodosa; but sometimes it is an autopsy diagnosis.

Hypertension, according to McGehee Harvey (1951), occurs in over 50 per cent of cases. It was present in 3 out of 10 patients in the series of Davson, Ball and Platt (1948) and in 9 out of 15 patients in the series of Spiegel (1936) and in 53 per cent of 177 cases from the literature reviewed by King (1950).

Often there is narrowing of large or of small renal blood vessels. Not all authors, however, find a close correlation between the amount of renal involvement and the height of the blood pressure. In some patients the blood pressure rises to great heights and the clinical and pathological changes characteristic of malignant hypertension make their appearance.

## Lupus Erythematosus

Hypertension is not a frequent complication of disseminated lupus erythematosus and when it occurs it is usually moderate in degree. In other ways lupus erythematosus may superficially resemble periarteritis nodosa, for the clinical manifestations of both depend upon the widespread involvement of arteries. Glomerulonephritis may be found in approximately 10 per cent of cases [191] but changes in the glomeruli due to the so-called wire loop lesions are much more frequent. Baehr et al (1935) found such changes in 13 out of 23 cases. Stickney and Keith (1940) found renal abnormalities in 7 out of 15 cases. Albumin, red cells and pus may be present in the urine and renal functions may be impaired

Shearn and Pirofsky (1952) encountered hypertension in 11 out of 34 cases of disseminated lupus erythematosus, 5 of them having associated renal disease In one patient the hypertension began during treatment with cortisone and persisted after it was discontinued. Heller et al (1951) found that haematuria and albuminuria persisted

during cortisone treatment of disseminated lupus. We had a similar experience with a man aged 37 who showed great improvement after ACTH and returned to his occupation as sheepfarmer. During 3 years albumin and red cells have usually been present in the urine. Nitrogen retention and moderate hypertension have both developed during this period of clinical remission and after withdrawal of ACTH therapy.

### Renal Lesions from Haemoglobinuria and Myoglobinuria

Haemolytic transfusion reactions may cause renal damage leading sometimes to anuria. Moderate rises of blood pressure occur. The mortality is high, a proportion of deaths occurring in uraemia, but when recovery occurs it is usually complete. Myoglobinuria may also cause acute renal damage and lead to death from uraemia. According to Baker and Dodds (1925) the pH of the urine is of decisive importance. Haemoglobin and myoglobin may remain in solution if the urine is alkaline, but become deposited in the tubules and may lead to uraemia if the pH lies between 4.5 and 6.1. The crush syndrome (Bywaters and Beall, 1941) is associated with the excretion of myoglobin in the urine (Bywaters and Stead, 1945). The blood pressure tends to rise above normal on recovery from the initial state of shock. According to Finkenstaedt et al. (1953) some defect of renal function may be present even four years after the crush syndrome. Hed (1955) describes moderate rises of blood pressure following episodes of myoglobinuria in three patients with familial paroxysmal myoglobinuria without muscular dystrophy. The two cases of idiopathic paroxysmal myoglobinuria described by Reiner et al. (1956) had hypertension (208/138 and 190/110 respectively). Additional information will be found in the monograph by Biorck (1949), where a number of rare and interesting disorders associated with myoglobinuria, and sometimes renal damage, are described.

### Renal Lesions from Multiple Myeloma

The lesions affect mainly the renal tubules which atrophy and may be replaced by fibrous tissue. The renal tubules may be obstructed by casts; the glomeruli may be normal or damaged. Hypertension according to Fishberg (1954) occurs in a small proportion of patients and may be coincidental. Nitrogen retention and even uraemia may occur.

### Polycystic Disease of the Kidneys

The majority of cases of polycystic disease of the kidneys exhibit hypertension. Although important interference with renal function is usually present the disease is usually much better tolerated than chronic glomerulonephritis and often it is present for many years without noticeable impairment in health. The kidneys are large and

palpable in almost all instances, though the enlargement is often more pronounced on one side than on the other. The condition is associated with marked cardiac hypertrophy and the course as regards the hypertensive disease resembles that of other hypertensive conditions. According to Schacht (1931) hypertension is present in 75 per cent of cases. In many instances death occurs from uraemia or intercurrent infection including intractable pyelonephritis.

### Syphilitic Disease of the Kidneys

Price and Skelton (1948) described the illness of a patient aged 24 who had exhibited hypertension starting in childhood, which led to death from heart failure. Autopsy showed a severe syphilitic aortitis and iliac aneurysms. The aorta at the level of the orifices of the renal arteries was distorted. Both renal arteries were almost occluded by intimal proliferation from extensive syphilitic arteritis and, although atheroma was also present, it was probably a secondary lesion. The authors point out the difficulty in interpreting the observations they made, but on the whole they think that the syphilitic aortitis was the cause of the hypertension.

Volhard (1931) describes syphilitic disease of the renal parenchyma associated with hypertension.

### Polycythaemia

According to Hurtado et al. (1945) and Lawrence et al. (1953) the polycythaemia of high altitudes is not associated with hypertension. "In polycythaemia vera approximately 50 per cent of the patients were found to be hypertensive by Lawrence et al (1953) but with very little relationship between blood pressure level and red cell count." These observations are of interest for in the few cases where cardiac outputs have been done they have been normal or even slightly raised. Hence, in high altitude polycythaemia the regulatory system must have compensated for increased blood viscosity by decrease of the peripheral resistance

### Hypertension from Congestive Heart Failure (*Hochdruckstauung*)

A high blood pressure occasionally falls with the onset of congestive heart failure but it may rise The French describe what they call "L'hypertension asystolique" and the Germans "Hochdruckstauung" (high pressure stasis). "The terms refer to elevation of the blood pressure in the course of cardiac insufficiency with its subsequent fall as the heart function improves.' The rise of blood pressure in the course of cardiac decompensation was first described by Sahli (1901) and later by Gallavardin

The use of [illegible]

with congestive heart failure by hexamethonium and thereby relieving the failure without the use of other medicaments, the blood pressure has stayed at a low level even when hexamethonium treatment was discontinued. This is an unusual reaction but confirms the view of Sahli and Gallivardin that sometimes heart failure may be the cause of blood pressure elevation.

### Hypertension in Beri-beri

An interesting survey of the literature has been published by Walters (1953) with an account of nine cases of acute cardiovascular beri-beri he saw personally among pearl divers in the Persian Gulf. The blood pressure exceeded 150/90 in four out of the nine cases and rose further in two of these cases on treatment with aneurin. The remaining five patients showed no hypertension on admission, but four of them developed a significantly raised blood pressure within four days of starting treatment. In most of the patients the blood pressures approached or exceeded 190/100 at some stage of the illness. Two of the patients died in pulmonary oedema. It would be valuable to know if such deaths could be averted by sitting the patient vertically with the legs down and administering fractional doses of hexamethonium intravenously until the blood pressure is slightly subnormal.

### Hypertension in Amputees

The French literature contains many references to the supposed increase in the incidence of hypertension among amputees. The literature is summarized in Traité de Médecine (1948). The report of a British committee (1955) on the subject stated that their investigation revealed no effect of amputation upon the incidence of cardiovascular disorders.

### Hypertension with Intermittent Claudication

Temporary rises of blood pressure during intermittent claudication were shown to occur by Malinow et al (1949). The blood pressure rises were the result of a blood pressure raising reflex from muscle (Alam and Smirk, 1938). They considered that blood pressure increases preceded the onset of pain.

### Hypertension in Emphysema

Geschickter and Popovici (1953) believe that there is an increased incidence of hypertension in patients with emphysema and bronchial asthma. They suggest that in emphysema the intraplural pressure is elevated, and this, being associated with elevation of the venous pressure, leads to renal congestion and a tendency to increased arterial pressure. The authors performed a lordosis test in the horizontal posture on the principle that, with lordosis, there is constriction of the inferior vena cava which may lead to renal congestion and secondary

changes in the blood pressure. They state that when they apply the lordosis test to normal people the blood pressure remains stationary or falls; in patients with borderline or fully developed hypertension both the systolic and the diastolic blood pressure rise, the diastolic pressure usually increasing by 15 mm. or more. It is, of course, possible that the rise of blood pressure represents an emotional response. Patients with emphysema and obesity, they find, get rises of blood pressure in the recumbent lordosis position, and in patients with emphysema it may be even more markedly elevated if the patients stand upright in a position of lumbar lordosis. The authors think that bad posture with abdominal obesity added on to emphysema is one of the factors which lead to hypertension in overweight people.

## Hypertension in Pink Disease

The manifestations of pink disease appear to be due, at least in part, to overactivity of the sympathetic and parasympathetic systems, the clinical manifestations being sweating, salivation, hypertension and peripheral vasoconstriction. While the blood pressure does not reach extraordinarily high levels, these are appreciably above the average for young children. In a series of 10 patients described by Bower (1954) the blood pressure was 135/90 or more in 6 patients. The patients were under 1 year of age

## Hypertension in Lead Poisoning

In recent years the opinion has gained ground that among industrial workers in lead there is no certain relation between hypertension and lead poisoning [143, 150, 236, 239, 327]. In the days when health precautions were rudimentary it was generally supposed that lead caused hypertension and arteriosclerosis Smith (1925) and Mayers (1928) found little to support the idea that lead promotes arteriosclerosis. Mayers found some evidence, however, of an increased incidence of hypertension in young workers in lead Pallor and active lead absorption both appeared more often among those workers having hypertension than among those who had no hypertension. In the tropical climate of Queensland, Australia, lead poisoning was at one time very common in children as lead paint on [illegible]
in the heat Hypertensi[illegible]
ing and is associated wi[illegible]
My own view is that un[illegible] circumstances lead poisoning causes hypertension

Lead poisoning has been referred to as leading on occasion to malignant hypertension by Fahr, (1919), Herxheimer (1924), and by Derow and Altschule (1935) One of our 50 cases of malignant hypertension had suffered from lead poisoning

## Miscellaneous Conditions

According to Gray (1954) hypertension is no more frequent in *mitral stenosis* cases than in controls. *Gout*, according to Brown and Mallory (1954) is associated with some increase in the incidence of hypertension. Urate deposits are often found in the renal medulla and fibrosis may occur. *Scleroderma* may be associated with marked renal lesions, leading in some instances to uraemia [322] and hypertension may result. *Steatorrhoea* is stated by Salvesen (1953) to be associated with subnormal blood pressures. Patients with *hernias* are less liable to essential hypertension according to Backer (1936), but the decrease in incidence did not seem to us to be significant in a group of patients with hernia examined in our hospital.

## *Hypertension in Children*

The causes of hypertension in children are fundamentally similar to those which occur in adults. The subject of juvenile hypertension has been admirably reviewed by McCrory and Nash (1952) who give many references. Genuine examples of juvenile essential hypertension are uncommon, unless we include comparatively minor elevations of the blood pressure to levels such as 140/90. Where there is substantial hypertension in a child there is likely to be some renal defect, such as glomerulonephritis or one of the many causes of interference with the renal circulation. It is especially important in children to investigate thoroughly the possibility of hypertension from unilateral renal disease, because in children there is a better chance of obtaining clinical improvement with a lasting reduction of the blood pressure. Most such cases are the result of unilateral pyelonephritis In children as well as in adults, unilateral renal ischaemia may be associated with malignant hypertension, and histologically, as in adults, arterioles may show medial necrosis and the onion skin appearance due to endothelial hyperplasia. The occurrence of these changes with unilateral renal disease in children supports the view that they are due to the blood pressure elevation. Bilateral pyelonephritis is a more frequent cause of hypertension than unilateral infection but, even so, only a small proportion of children with proved pyelonephritis exhibit hypertension Phaeochromocytoma, Cushing's syndrome and thyrotoxicosis are occasional causes of raised blood pressure in children. Systolic hypertension may occur with patent ductus arteriosus or with aortic regurgitation. Aortic coarctation is an important possibility in a child with an unexplained hypertension, Bulbar poliomyelitis and other bulbar lesions may cause hypertension in children as they do in adults. In Queensland, Australia, lead poisoning was at one time an important cause of hypertension in children. As in adults, many instances of moderate blood pressure increase in children are the result of nervousness, and slightly higher blood pressure measurements are found in obese children. There are

several publications relating to hypertension in children [10, 12, 74, 80, 163, 173, 183, 195, 266, 287, 317], but few provide more than a few case histories.

Reis and Chaloupka (1923) state that for several days after delivery the blood pressures may be raised in at least some cases where labour has been difficult, for example, some forceps cases. Trauma to the foetal head may also be associated with a rise of blood pressure. Additional references to hypertension in children are made earlier in this chapter, especially in the section on unilateral renal disease.

## References


1 Adams, L. J, Notkin, M., and Pritchard, J. E. Hypertension in two cases of renal artery occlusion Canad. med. Ass J., 64: 224, 1951.

1a Adams, L. J Hypertension and unilateral kidney disease: Late results of nephrectomy in seven patients Canad. med Ass. J., 73: 800, 1955.

2 Alam, M, and Smirk, F. H Observations in man upon a blood pressure raising reflex arising from the voluntary muscles J Physiol. (Lond.), 89. 372, 1937

3 Alam, M, and Smirk, F H Observations in man on a pulse-accelerating reflex from the voluntary muscles of the legs. J Physiol. (Lond.), 92 167, 1938a

4 Alam, M, and Smirk, F H Blood pressure raising reflexes in health, essential hypertension, and renal hypertension. Clin. Sci, 3: 259, 1938b

5 Alesandri, H, and Roeschmann, W Glomerulo nefritis aguda sin sindrome urinario Rev méd Chile, 70: 408, 1951.

6 Allen, A C The clinicopathologic meaning of the nephrotic syndrome. Amer J Med, 18. 277, 1955

7 Arneil, G C, and Dekanski, J B Excess of vasopressor activity in plasma of nephritic children [illegible]

8 Arnold, M W, Goodwin, [illegible] and its relation to hy[illegible]

9 Arons, W L, Christensen [illegible] visible by x-ray assoc[illegible] intern Med, 42 260, 1955.

10 Aronson [illegible] simu[illegible]

11 Aronson [illegible] unila[illegible] cont[illegible] [illegible] Arch Path. (Chicago), 51 30, 1951

12 [illegible]

13 Audier, M, Taddei, A, and Rasmussen, C Sur un cas d'hypertension artérielle permanente consécutive à un traumatisme cranien Arch Mal Coeur, 43. 379, 1950

14 Baehr, G, Klemperer, P., and Schifrin, A. A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis) Trans Ass Amer. Phys, 50: 139, 1935

15 Backer, M Essential hypertension II Constitutional considerations Amer J med Sci, 192. 395, 1936

16 BAHNSON, H. T., COOLEY, R N., and SLOAN, R. D. Coarctation of the aorta at unusual sites: report of two cases with angiocardiographic and operative findings. Amer. Heart J., 38: 905, 1949.
17 BAIRD, D., and DUNN, J. S Renal lesions in eclampsia and nephritis of pregnancy. J. Path. Bact., 37: 291, 1933.
18 BAKER, A. B. Neurologic signs of bulbar poliomyelitis Poliomyelitis, Papers and Discussions presented at the First International Poliomyelitis Conference J. B. Lippincott Company, Philadelphia, p. 241, 1949
19 BAKER, S. L., and DODDS, E. C. Obstruction of the renal tubules during the excretion of haemoglobin. Brit. J. exp. Path, 6: 247, 1925
20 BARCROFT, J. Researches on pre-natal life. Blackwell, Oxford, 1946
21 BARKER, N W, and WALTERS, W. Hypertension and chronic atrophic pyelonephritis. Proc. Mayo Clin, 15: 475, 1940
22 BARKER, N. W., and WALTERS, W. Hypertension and chronic atrophic pyelonephritis — Results of nephrectomy J. Amer. med. Ass, 115 912, 1940.
23 BARNESS, L A, MOLL, G H, and JANEWAY, C A. Nephrotic syndrome. I. Natural history of the disease Pediatrics, 5: 486, 1950
23a BARNES, A C, and QUILLIGAN, E J Measurements of aldosterone in the eclamptogenic toxemias of pregnancy Amer J. Obstet. Gynec, 71. 670, 1956
24 BARNETT, A. J The action of benzodioxane. Lancet, 2: 73, 1950
25 BARTHOLOMEW, R A, and KRACKE, R R The relation of placental infarcts to eclamptic toxemia — A clinical, pathologic, and experimental study. Amer J. Obstet. Gynec., 24. 797, 1932.
26 BASTIAANSE, M. A VAN B Etiological aspects in the problem of toxemia of pregnancy Amer J Obstet Gynec, 68: 151, 1954
26a BASTIAANSE, M A VAN B., and MASTBOOM, J L Kidney and pregnancy with an experimental part concerning the ischaemia of the gravid uterus in dogs Gynaecologia (Basel), 127, 1, 1949.
27 BAUER, H, and FORBES, G L Unilateral renal artery obstruction associated with malignant nephrosclerosis confined to the opposite kidney Amer. Heart J, 44 634, 1952
28 BAUER, J. L'influence des surrénales et de l'hypophyse sur la régulation de la pression artérielle et sur la transformation des caractères sexuels chez l'homme Arch int méd exp, 9: 395, 1935.
29 BAUER, J, and BELT, E Paroxysmal hypertension with concomitant swelling of the thyroid due to pheochromocytoma of the right adrenal gland — Cure by surgical removal of the pheochromocytoma J clin Endocr, 7: 30, 1947
30 BECHGAARD, P Arterial hypertension — A follow-up study of one thousand hypertonics Acta med. scand, suppl. 172 1, 1946
31 BELL, E T. Renal lesions in the toxemias of pregnancy. Amer J Path, 8. 1, 1932
32 BELL, E. T A clinical and pathological study of subacute and chronic glomerulonephritis, including lipoid nephrosis Amer J Path., 14. 691, 1938
33 BELL, E T Exudative interstitial nephritis (pyelonephritis) Surgery, 11. 261, 1942
34 BEN-ASHER, S Hypertension caused by renal infarction Ann intern Med, 23 431, 1945.
35 BERLIN, N I, HYDE, G. M., LAWRENCE, J H, PARSONS, R J, and PORT, S The blood volume in pre-eclampsia as determined with P[32] labelled red blood cells Surg Gynec Obstet, 94 21, 1951

36 [illegible]

37 [illegible]

38 BLACK, D. A. K., PLATT, R., ROWLANDS, E. N., and VARLEY, H. Renal haemodynamics in acute nephritis. Clin Sci, 6: 295, 1948

39 BLACKMAN, S. S. Jr. Arteriosclerosis and partial obstruction of main renal arteries in association with essential hypertension in man. Bull Johns Hopk Hosp, 65: 353, 1939

40 BLAND, W. H., MARCUS, R., and WASSERMAN, D. M. A case of malignant hypertension secondary to renal ischaemia. Ann. intern Med, 37: 179, 1952

41 [illegible]

4[illegible] [illegible] 20 681, 1952.

42 BOLT, W., VALLENTIN, H., and VENRATH, H. Über die Ätiologie des Hochdruckes bei Atemmuskelgelähmten Dtsch Arch klin. Med, 198 474, 1951.

43 BORS, E., and FRENCH, J. D. Management of paroxysmal hypertension following injuries to cervical and upper thoracic segments of the spinal cord Arch Surg (Chicago), 64· 803, 1952

44 BOURNE, W. A. Nephrectomy in hypertension due to renal artery infarction with superinfection of streptococcal endocarditis by fungus. Brit med J, 2 271, 1954

45 BOWER B. D. Pink disease — The autonomic disorder and its treatment with ganglion-blocking agents Quart J Med., 23: 215, 1954

46 BOYLE, H. H., and HEBERT, H. J. Chronic nephritis and nephrosis in children Med Clin N Amer, 34 71, 1950.

47 BRAASCH, W. F. The surgical kidney as an etiological factor in hypertension Canad med. Ass J, 46 9, 1942

48 BRAASCH, W. F., and JACOBSON, C. E. Chronic bilateral pyelonephritis and hypertension Proc. Mayo Clin, 15· 481, 1940

49 BRAASCH, W. F., and JACOBSON, C. E. Chronic bilateral pyelonephritis and hypertension J Urol (Baltimore), 44 571, 1940

50 BRAASCH, W. F., WALTERS, W., and HAMMER, H. J. Hypertension and the surgical kidney. Proc Mayo Clin, 15· 477, 1940

51 BRAUN-MENENDEZ, E. The thyroid in experimental renal hypertension Abstract of Papers, Second World Congress of Cardiology, Washington, D.C. 1954, p 360

52 BREBNER, H. Dissecting aneurysm of the aorta with renal complications Brit, med J 1: 394, 1951

52a BROD, J. Chronic pyelonephritis and hypertension Acta med scand, suppl 312 122 1956.

53 BROWN, J., and MALLORY, G. K. Renal changes in gout New Engl J. Med, 243· 325, 1950.

54 BROWN, M. R., CURRENS, J. H., and MARCHAND, J. F. Muscular paralysis and electrocardiographic abnormalities — Resulting from potassium loss in chronic nephritis J Amer med. Ass, 124. 545, 1944

55 BROWNE, F. J., and DODDS, G. H. The remote [illegible] of pregnancy based on a follow-[illegible] nancies for periods varying fro[illegible] Gynaec Brit Emp, 46 443, [illegible]

56 BROWNE, J. C. McC., and VEALL, N. The maternal placental blood flow

in normotensive and hypertensive women. J. Obstet. Gynaec. Brit. Emp., 60: 141, 1953

57 Bruck, E., Rapoport, M., and Mitchell, I. R. Renal functions in the course of the nephrotic syndrome in children J. clin. Invest., 33: 699, 1954

58 Burchell, H. B., Taylor, B. E., Knutson, J. R. B., and Wakim, K. G. Direct blood pressure determinations and comparative arm blood flows in subjects with coarctation of the aorta, the stricture being proximal to origin of left subclavian artery. Amer. J. Med., 8: 810, 1950.

59 Butler, A. M. Chronic pyelonephritis and arterial hypertension. J. clin Invest., 16: 889, 1937.

60 Bywaters, E. G. L., and Beall, D. Crush injuries with impairment of renal function. Brit med. J., 1: 427, 1941.

61 Bywaters, E. G. L., and Stead, J. K. The production of renal failure following injection of solutions containing myohaemoglobin Quart. J exp Physiol., 33: 53, 1945—46

62 Calkins, E., Dana, G. W., and Howard, J. E. Current methods of diagnosis of pheochromocytoma J. Amer. med. Ass., 145: 880, 1951.

63 Calkins, E., and Howard, J. E. Bilateral familial phaeochromocytoma with paroxysmal hypertension: successful surgical removal of tumours in two cases, with discussion of certain diagnostic procedures and physiological considerations. J. clin Endocr., 7: 475, 1947.

64 Chinard, F. P., Lauson, H. D., Eder, H. A., Greif, R. L., and Hiller, A. A study of the mechanism of proteinuria in patients with the nephrotic syndrome J clin Invest., 33: 621, 1954

65 Clark, A. M., and Skillern, P. G. Intercapillary glomerulosclerosis — Pathogenic and clinical features and treatment, based on study of 100 cases. Med Clin N Amer., 39: 1001, 1955.

66 Clemetson, C. A. B., and Churchman, J. Oxygen and carbon dioxide content of umbilical artery and vein blood in toxaemic and normal pregnancy J Obstet Gynaec Brit Emp., 60: 335, 1953

67 Cohen, M. Addison's disease complicated by toxemia of pregnancy. Arch intern. Med., 81: 879, 1948.

68 Colston, J. A. C. Surgical aspects of bilateral familial pheochromocytoma. J Urol (Baltimore), 59: 1036, 1948

69 Commons, R. R., and Callaway, C. P. Adenomas of the adrenal cortex Arch intern Med., 81: 37, 1948

69a Conn, J. W. Primary aldosteronism, a new clinical syndrome J. Lab clin Med., 45: 6, 1955

70 Corry, D. C. Hypertension in ruptured kidney. Brit med J., 1: 433, 1946

71 Cossio, P., Arana, R., and Kreutzer, R. Alteraciones del electrocardiograma en la glomerulonefritis difusa aguda. Rev argent Cardiol., 6. 283, 1939

72 Cox, L. W., and Chalmers, T. A. The effect of pre-eclamptic toxaemia on the exchange of sodium in the body and the transfer of sodium across the placenta, measured by $Na^{24}$ tracer methods J. Obstet Gynaec Brit Emp., 60: 215, 1953

73 Crabtree, E. G. Pyelonephritic injuries to the kidneys and their relation to hypertension. J. Urol. (Baltimore), 44: 125, 1940.

74 Craig, J. Malignant hypertension in childhood Arch Dis. Child., 6. 157, 1931.

75 Crofton, J., and Truelove, L. Apparent acute glomerulonephritis without albuminuria — Report of a case Lancet, 2: 54, 1948

76 Cross, G. O., Lusignan, F. W., and Pace, J. W. Paroxysmal hypertension

secondary to malignant pheochromocytoma — Report of a case and review of the literature. Calif. Med., 74: 392, 1951.

77 CUNNINGHAM, G. J. Intestinal lesions in malignant hypertension with report of a case Brit. med. J., 1: 1075, 1948.

78 DAVIDSEN, H. G., KJERULF-JENSEN, K., and KRARUP, N. B. Treatment of chronic renal potassium deficiency. Lancet, 1: 375, 1951.

79 DAVIES, D. F., and CLARK, H. E. A hypertensive syndrome with relative adrenal cortical overactivity. Circulation (N.Y.), 2: 494, 1950

80 DAVIES, D. M. Cushing's Syndrome in a child of 2½ years Proc. roy. Soc. Med., 46: 307, 1952.

81 DAVIES-COLLEY, N. Bones and kidneys from a case of osteomalacia in a girl aged 13. Trans path. Soc Lond., 35. 286, 1884.

82 DAVIS, P., PEART, W. S., and HOFF, W. V. Malignant phaeochromocytoma with functioning metastases. Lancet, 2. 274, 1955.

83 DAVSON, J. Malignant hypertension associated with hydatid disease of the kidney J. Path Bact., 53: 207, 1941.

84 DAVSON, J., BALL, J., and PLATT, R. The kidney in periarteritis nodosa. Quart J. Med., 41. 175, 1948

85 DAVSON, J., and PLATT, R. A clinical and pathological study of renal disease I Nephritis Quart. J Med., n.s 18: 149, 1949.

86 DAWSON, B The prevention of eclampsia — An Australasian experiment J Obstet Gynaec Brit Emp., 60 80, 1953

87 DEAN, A. L., and ABELS, J. C. Study by the newer renal function tests of an unusual case of hypertension following irradiation of one kidney and the relief of the patient by nephrectomy J. Urol (Baltimore), 52. 497, 1944

88 DE NAV[illegible]

89 [illegible]

90 [illegible]

91 DEXTER, L., and HAYNES, F. W. Relation of renin to human hypertension with particular reference to eclampsia, preeclampsia and acute [illegible]

92 DE [illegible]

93 DIECKMANN, W. J. The toxemias of pregnancy The C. V. Mosby Company, St Louis, 1952, 2nd edn

94 DINGLE, J. H., RAMMELKAMP, C. H., Jr., and WANNAMAKER, L. W. Epidemiology of streptococcal infections and their non-suppurative complications Lancet, 1: 736, 1953.

95 DOUMER, E., LORRIAUX, A. [illegible] due to aplasia of the [illegible] abdominal aorta — [illegible] Coeur, 44 446, 1951

96 DOYLE, A. F. [illegible] suppl. [illegible]

97 DRILL, V. A [illegible] of phe[illegible]

98 DUVAL, C [illegible] glomer[illegible] and a [illegible] report [illegible]

99 Duval, C. W., and Hibbard, R. J. Experimental glomerulonephritis induced in rabbits with the endotoxic principle of streptococcus scarlatinal J. exp. Med., 44: 567, 1926b

100 Earle, D. P., Jr. Renal function tests in the diagnosis of glomerular and tubular disease. Bull. N.Y. Acad. Med, 26: 47, 1950.

101 Earle, D. P., Jr., Farber, J. D. ...
E. D. Renal f
nephritis. J.

102 Earle, D. P., Jr., Sherry, S., Eichna, L. W., and Conan, N J Low potassium syndrome due to defective renal tubular mechanisms for handling potassium. Amer. J Med., 11: 283, 1951.

103 Earle, D. P., Jr., Taggart, J. V., and Shannon, J A. Glomerulonephritis — A survey of the functional organization of the kidney in various stages of diffuse glomerulonephritis J clin Invest, 23: 119, 1944

104 Eisenberg, A. A, and Wallerstein, H Pheochromocytoma of the suprarenal medulla (Paraganglioma) — A clinicopathologic study. Arch Path. (Chicago), 14: 818, 1932

105 Eisenberg, S, Buie, R, Jr., and Tobian, L., Jr Adrenal cortical function in essential hypertension — A study of sweat sodium concentration. Amer. J. med. Sci., 220: 287, 1950

106 Elkinton, J R, Tarail, R, and Peters, J. P. Transfers of potassium in renal insufficiency. J. clin. Invest, 28: 378, 1949.

107 Ellis, A. Natural history of Bright's Disease — Clinical, histological and experimental observations Lancet, 1: 1, 1942.

108 Ellis, A. Natural history of Bright's disease — Clinical, histological and experimental observations III. The vicious circle in chronic Bright's disease. Lancet, 1: 72, 1942.

109 Ellis, A. W. M. Pathogenesis of renal lesions in Bright's disease. Arch. intern. Med, 84: 159, 1949

110 Engel, A, and von Euler, U. S Diagnostic value of increased urinary output of noradrenaline and adrenaline in phaeochromocytoma Lancet, 2: 387, 1950

111 Engel, W J, and Page, J H Hypertension due to renal compression resulting from subcapsular hematoma J Urol (Baltimore), 73· 735, 1955

111a Epstein, F. H, and Zupa, V J. Clinical correlates of the Kimmelstiel-Wilson Lesion New Engl J Med., 254. 896, 1956

111b Evans, B M, and Milne, M. D Potassium-losing nephritis presenting as a case of periodic paralysis Brit med J, 2 1067, 1954.

112 Evans, J A, Rubitsky, H J, Bartels, C C, and Bartels, E C Re-evaluation of the reliability of pharmacologic and cold pressor studies in hypertension and pheochromocytoma Amer J Med, 11 448, 1951

113 Fahr Die Eklampsie Bonn, 1924 Cited by Fishberg, A M, "Hypertension and Nephritis", Lea and Febiger, Philadelphia, 1954, 5th edn

114 Fahr, G E The mechanism of hypertension in chronic genuine nephrosis. "Hypertension", edited by Bell, E T, University of Minnesota Press, Minneapolis, 1951

115 Fahr, T Über Nephrosklerose Virchows Arch path Anat, 226 119, 1919

115a Farrell, G L, Rosnagle, R S, and Rauschkolb, E W Aldosterone secretion during bleeding Fed Proc, 15 60, 1956

116 Finkenstaedt, J T., O'Meara, H P, Weller, J M, and Merrill, J P Renal function after recovery from acute renal failure J clin Invest, 32: 567, 1953.

117 FINNERTY, F. A., Jr. Does vascular damage follow toxemia of pregnancy? An internist's appraisal of three hundred and three patients in a toxemia clinic. J. Amer. med. Ass, 154: 1075, 1954.

118 FISHBERG, A. M. Hypertension due to renal embolism. J. Amer med. Ass, 119: 551, 1942

119 FISHBERG, A. M Hypertension and Nephritis, Lea and Febiger, Philadelphia, 1954, 5th edn.

120 FISHER, E. R., and CORCORAN, A. C Congenital coarctation of the abdominal aorta with resultant renal hypertension Arch intern. Med., 89. 913, 1952

121 FISHER, J A, and HEWER, T F The adrenal cortex in essential and renal hypertension J Path. Bact, 59· 605, 1947.

122 FLETCHER, M. H. Case of infantilism with polyuria and chronic renal disease Proc. roy. Soc. Med, 4· 95, 1911.

123 FRÄNKEL, F. Ein Fall von doppelseitigem, völlig latent verlaufenen Nevennierentumor und gleichzeitiger Nephritis mit Veränderungen am circulations-apparat und Retinitis Virchows Arch path. Anat., 103 244, 1886

124 FREEMAN, G, and HARTLEY, G, Jr Hypertension in a patient with a solitary ischemic kidney J Amer med. Ass, 111: 1159, 1938.

125 FREIS, E D, and KENNY, J F Plasma volume, total circulating protein, and "available fluid" abnormalities in preeclampsia and eclampsia. J clin Invest, 27: 283, 1948.

126 GAYMAN, M, NASSIF AMIN, and SMIRK, F H. Casual and basal blood pressures III In renal hypertension Brit. Heart J., 5: 161, 1943.

127 GAULD, W R, STALKER, A L, and LYALL, A Renal complications in diabetes mellitus with special reference to the Kimmelstiel-Wilson lesion Brit med J, 2 194, 1948

127a GENEST, J, LEMIEUX, G., DAVIGNON, A, KOIW, E., NOWACZYNSKI, W., and STEYERMARK, P Human arterial hypertension· A state of mild chronic hyperaldosteronism Science, 123. 503, 1956

128 GESCHICKTER, C F, and POPOVICI, A Phrenic or postemphysematous hypertension Arch intern Med, 92 767, 1953.

129 GIBSON, A G Pyelitis and pyelonephritis. Lancet, 2: 903, 1928.

130 GIBSON, G G The clinical significance of the retinal changes in the hypertensive toxemias of pregnancy Amer J Ophthal., 21: 22, 1938.

131 GIFFORD, R W, Jr, ROTH, G M, and KVALE, W. F. Evaluation of new adrenolytic drug (Regitine) as test for pheochromocytoma. J. Amer. med Ass., 149. 1628, 1952.

132 GOLDEN, A, DEXTER, L., and WEISS, S Vascular disease following toxemia of pregnancy (preeclampsia and eclampsia) Arch. intern. Med, 72· 301, 1943

133 GOLDENBERG, M, ARANOW, H, Jr, SMITH, A. A, and FABER, M. Pheochromocytoma and essential hypertensive vascular disease Arch intern Med, 86 823, 1950

134 GOLDENBERG, M, SERLIN, I, EDWARDS, T, and RAPPORT, M. M. Chemical screening methods for the diagnosis of pheochromocytoma. I. Norepinephrine and epinephrine in human urine. Amer. J. Med, 16. 310, 1954

135 GOLDRING, W, and CHASIS, H Hypertension and hypertensive disease. The Commonwealth Fund, New York, 1944.

136 GOODMAN, H L Malignant hypertension with unilateral renal artery occlusion New Engl J Med, 246 8, 1952

137 GORDON, D M Routine examination of the ocular fundi as an aid in

*management of toxemias of pregnancy*. J. Amer. med. Ass., 146 810, 1951.

137a GRABER, I. G., and SHACKMAN, R. Divided renal function studied in hypertension. Brit. med. J., 1: 1321, 1956.

138 GRAM, H. C. A symptom-triad of the post-climacteric period (Adipositas dolorosa — Arthritis genuum — Hypertensio arterialis) Acta med. scand., *73: 139, 1930*

139 GRANT, R. T., and REEVE, E. B. Observations on the general effects of injury in man: with special reference to wound shock. Medical Research Council Special Report No 277. Her Majesty's Stationery Office, London, 1951

140 GRAY, I R. Mitral stenosis and hypertension. Brit. Heart J., 16: 165, 1954.

141 Great Britain Ministry of Pensions (Sir Ernest Rock Carling, Chairman of Committee). Report on cardiovascular disorders and mortality rates in amputees. Brit. med. J., 1: 102, 1955.

142 GREEN, D. M. Pheochromocytoma and chronic hypertension J. Amer. med. Ass., *131· 1260, 1946*

143 GREENFIELD, I, and GRAY, I. Lead poisoning IX. The failure of lead poisoning to affect the heart and blood vessels. Amer. Heart J, 39. 430, 1950

144 GRIFFITHS, A. L. Hypertension of renal origin in childhood Arch Dis Childh, *25. 81, 1950*

144a GROSS, F, LOUSTALOT, P., and MEIER, R. Vergleichende Untersuchungen über die hypertensive Wirkung von Aldosteron und Desoxycorticosteron Experientia (Basel), 11: 67, 1955

145 GRULEE, C. G. Jr, and PANOS, T. C Epidemic poliomyelitis in children — Clinical study, with special reference to symptoms and management of bulbar polioencephalitis. Amer J *Dis Child*, *75· 24, 1948*

146 GUTMANN, D. Medullary suprarenal chromaffinoma producing malignant *hypertension Brit med J, 1. 503, 1947*

147 GUTTMANN, L, and WHITTERIDGE, D Effects of bladder distension on autonomic mechanisms after spinal cord injuries Brain, 70 361, 1947

148 HAIMOVICI, H Evidence for an adrenergic component in the nervous mechanism of sweating in man Proc Soc exp Biol (N Y), 68 40, 1948

149 *HALLUM, A V Eye changes in hypertensive toxemia of pregnancy*; a study of three hundred cases J. Amer med Ass, 106 1649, 1936

150 HAMILTON, A, and JOHNSTONE, R T Industrial Toxicology Oxford University Press, New York, 1945

150a HAMILTON, G R, GETZ, R J, and JEROME, S Arteriovenous fistula of the renal vessels Case report and review of the literature J Urol (Baltimore), *69· 203, 1953*

151 HAMILTON, J D, and FREMES, N E The natural history of experimental glomerulonephritis produced by foreign protein Amer J Path, 30 127, 1954

152 HAMLIN, R H J The prevention of eclampsia and pre-eclampsia Lancet, 1. 64, 1952

153 HAMLIN, R H J. The prevention of pre-eclampsia by means of diet and weight-control (synopsis). Proc. roy Soc Med, 46. 393, 1953

154 HARDING, V T, and VAN WYCK, H B Diet in the treatment of pre-eclampsia J Obst. Gynaec. Brit Emp, 33 17, 1926

155 HEAD, H, and RIDDOCH, G. The automatic bladder, excessive sweating and some other reflex conditions, in gross injuries of the spinal cord Brain, 40: 188, 1917

156 HED, R. Myoglobinuria in man with special reference to a familial form.

Chap V. Three cases of familial paroxysmal myoglobinuria without muscular dystrophy. Acta med scand, suppl. 303 5, 1955
157 HEINTZ, R., LOSSE, H, and GÖRLITZ, F. Ungewöhnliche Formen renaler Hypertonie Münch. med Wschr., 96: 4, 1954a; ibid, 96: 33, 1954b.
158 HELLER, B I, JACOBSON, W. E., and HAMMARSTEN, J F The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosus J. Lab. clin. Med, 37: 133, 1951.
159 HELPS, E. P. W., ROBINSON, K. C., and ROSS, E. J. Phentolamine in the diagnosis and management of phaeochromocytoma. Lancet, 2: 267, 1955
159a HENDERSON, D A. Chronic nephritis in Queensland. Aust. Ann. Med, 4: 163, 1955.
160 HEPTINSTALL, R H. Malignant hypertension: A study of fifty-one cases J Path Bact., 65 423, 1953
161 HERXHEIMER, G Über Arteriolonekrose der Nieren Virchows Arch path Anat., 251 709, 1924
162 HEYMANN, W, and LUND, H. Z. Nephrotic syndrome in rats Pediatrics, 7 691, 1951
163 HOAG, L Malignant hypernephroma in children. Amer. J. Dis. Child., 25 441, 1923
164 HOFFMAN, B J Renal ischemia produced by aneurysm of abdominal aorta J Amer, med Ass, 120 1028, 1942
164a HOLLINGSWORTH, E W Arteriovenous fistula of the renal vessels Amer J med Sci, 188 399, 1934
165 HOLTZ, P, CREDNER, K and KRONEBERG, G Über das sympathicomimetische pressorische Prinzip des Harns ("urosympathin"). Arch. exp. Path Pharmak, 204. 228, 1947
166 HOOBLER, S W, AGREST, A, and WARZYNSKI, R. J. Biochemical determination of blood and urine catechol amines as a measure of sympathoadrenal activity in hypertension J clin Invest., 33: 943, 1954.
167 HORTON, B T The relationship of hypertension to renal neoplasm Proc Mayo Clin, 15 472, 1940
168 HOWARD, J E, BERTHRONG, M, GOULD, D M, and YENDT, E. R Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy Bull Johns Hopk Hosp, 94: 51, 1954.
169 HOWARD, J M., ARTZ, C P, and STAHL, R R. The hypertensive response to injury (the systemic response to injury) Ann Surg, 141: 327, 1955a
170 HOWARD, J M, OLNEY, J. M, FRAWLEY, J P, PETERSON, R. E, SMITH, L H, DAVIS, J H, GUERRA, S., and DIBRELL, W. H. Studies of adrenal function in combat and wounded — A study in the Korean theatre Ann Surg, 141. 314, 1955b.
171 HOWARD, T. L, FORBES, R P., and LIPSCOMB, W. R Aneurysm of the left renal artery in a child five years old with persistent hypertension. J Urol (Baltimore), 44: 808, 1940
172 HURTADO, A, MERINO, C., and DELGADO, E Influence of anoxemia on the hemopoietic Arch intern Med, 75 284, 1945.
173 HUTCHISON, R, and MONCRIEFF, A A case of primary hypertension in a child Brit J Child Dis, 27. 201, 1930
174 HYMAN, A, and MENCHER, W. H Pheochromocytoma of the adrenal gland J. Urol (Baltimore), 49: 755, 1943
175 IMBER, I, and CLYMER, R H, Jr. Obstruction of the renal artery producing malignant hypertension New Engl J. Med, 252 301, 1955
176 ISENHOUR, C E, KUDER, K, and DILL, L. V The effect of parity on the

O

average blood pressure and on the incidence of hypertension. Amer. J. med. Sci, *203: 333, 1942.*

177 JOINER, C L., and THORNE, M G On the [illegible]

178 JONE [illegible]

179 KEITH, N. M., KING, H. E., and OSTERBERG, A. E. Serum concentration and renal clearance of potassium in severe renal insufficiency in man Arch. intern. Med., **71**: 675, 1943.

180 KEITH, N. M., and ODEL, H. M Outlook for patients with glomerulonephritis J. Amer. med. Ass, **153**· 1240, 1953.

181 KELSALL, A. R., and ROSS, E J. Bilateral phaeochromocytoma in two sisters. Lancet, **2**: 273, 1955.

182 KENNEDY, R. L. J. The pathologic changes in pyelitis of children interpreted on the basis of experimental lesions *J. Urol. (Baltimore)*, **27**. 371, 1932

183 KERLEY, C. G, and LORENZE, E. J. *Blood pressure observation on children* in private practice. J. Pediat, **20**: 383, 1942.

184 KESSLER, E *Hypercalcemia and renal insufficiency secondary to excessive* milk and alkali intake. Ann intern. Med., **42**: 324, 1955

185 KEZDI, P. *Neurogenic hypertension in man in porphyria* — Transient hypertension and tachycardia caused by disruption of the carotid *sinus. Review of buffer nerve mechanism* Arch intern Med, **94**. 122, 1954

186 KIMMELSTIEL, P., and WILSON, C Benign and malignant hypertension and nephrosclerosis — A clinical and pathological study Amer J. Path, **12**· 45, 1936a

187 KIMMELSTIEL, P, and WILSON, C. Intercapillary lesions in the glomeruli of the kidney Amer J Path, **12**· 83, 1936b

188 KING, B G The clinical diagnosis of periarteritis nodosa — Report of four cases Ann intern Med, **32**· 466, 1950

189 KINNEY, T D, and MALLORY, G K. Personal communication Cited by Mansfield, J S, MALLORY, G K, and ELLIS, L B, New Engl J Med **229**· 387, 1943

189a KIRBY, C K, NICHOLS, W G, GARRITANO, A P, WOHL, G T, and PIETROLUONGO, A. L Arteriovenous fistula of the renal vessels· A case report Surgery, **37**. 267, 1955

190 KIERULF-JENSEN, K, KRARUP, N B, and WARMING-LARSEN, A Persistent hypokalaemia requiring constant potassium therapy Lancet, **1**. 372, 1951

191 KLEMPERER, P, POLLACK, A D., and BAEHR, G Pathology of disseminated *lupus erythematosus. Arch. Path (Chicago)*, **32** 569, 1941.

192 KOEPSELL, J E, KUZMA, J. F, and MURPHY, F D. Hypertensive Cardiovascular *Disease (acute) (malignant hypertension)* — Clinical and pathologic study of thirty-nine cases Arch intern Med, **85** 432, 1950.

193 KOONS, K. M., and RUCH, M. K Hypertension in a 7 year old girl with Wilms' tumor relieved by nephrectomy J Amer med Ass, **115**· 1097, 1940

194 KREMER, D N. Medullary tumor of the adrenal glands with hypertension and juvenile arteriosclerosis Arch. intern Med, **57**: 999, 1936

195 KÜHNS, K, and HÖPFNER, K Differentialdiagnose des jugendlischen Hochdrucks. Dtsch. Arch. klin Med, **200**. 7, 1952

196 KVALE, W. F, PRIESTLEY, J. T, and ROTH, G. M Pheochromocytoma — *Clinical aspects and surgical results*, Arch Surg, **68** 769, 1954

197 LABBÉ, M, TINEL, J, and DOUMER, E Crises solaires et hypertension

paroxystique en rapport avec une tumeur surrénale. Bull Soc. méd Hôp. Paris, 46: 982, 1922
198 LACHMUND, H Hochdruk bei Poliomyelitis Dtsch med. Wschr, 75: 450, 1950
199 LAFORET, E. G. Malignant hypertension associated with unilateral renal artery occlusion: three cases. Ann. intern Med, 38: 667, 1953.
200 LAMPEN, H. Experimentelle Sinusblockade bei den verschiedenen Hochdruckformen. Verh dtsch. Ges. Kreisl Forsch Steinkopff, Frankfurt, 1949
201 LANGLEY, G. J., and PLATT, R. Hypertension and unilateral kidney disease Quart J. Med, n s. 16: 143, 1947.
202 LAUSON, H D, FORMAN, C W., MCNAMARA, H, MATTAR, G, and BARNETT, H L The effect of corticotropin (ACTH) on glomerular permeability to albumin in children with the nephrotic syndrome J. clin Invest, 33: 657, 1954
203 LAWRENCE, J H, BERLIN, N I., and HUFF, R. L The nature and treatment of polycythemia—Studies on 263 patients Medicine (Baltimore), 32: 323, 1953.
204 LEADBETTER, W. F., and BURKLAND, C E Hypertension in unilateral renal disease J. Urol. (Baltimore), 39: 611, 1938
205 LINDBERG, H A Management of glomerulonephritis Gen. Practit, 4: 71, 1951
205a LLAURADO, J G Further studies on the excretion of aldosterone following surgical trauma Proc. Univ. Otago med Sch., 33: 10, 1955
206 LÖBLICH, H J Lage und Funktion des blutdruckregulierenden Zentrums in der Medulla Oblongata (nach befunden bei Poliomyelitis) Virchows Arch. path Anat., 318: 211, 1950.
207 LOEB, R F The adrenal cortex and electrolyte behavior. Bull N.Y. Acad Med, 18: 263, 1942.
208 LOGE, J P, LANGE, R. D, and MOORE, C. V. Characterization of the anemia of chronic renal insufficiency J. clin. Invest., 29. 830, 1950
209 LOHMANN, V Über Diabetes Mellitus bei Nebennierenmarktumoren Dtsch med. Wschr, 75 138, 1950
210 LONGCOPE, W. T Chronic bilateral pyelonephritis its origin and its association with hypertension Ann intern. Med, 11. 149, 1937.
210a LUETSCHER, J A, Jr, and AXELRAD, B J Increased aldosterone output during sodium deprivation in normal men. Proc. Soc exp Biol (N Y), 87: 650, 1955.
210b LUETSCHER, J A., Jr, and JOHNSON, B. B. Observations on the sodium-retaining corticoid (aldosterone) in the urine of children and adults in relation to sodium balance and edema J. clin. Invest, 33: 1441, 1954
211 LUFT, R, and SJÖGREN, B. Gynecomastia, hypertension, decreased dextrose and increased insulin tolerance in [illegible]
212 McC [illegible] hypertension in children: A review. Amer J med. Sci, 223 671, 1952.
213 MCCULLAGH, E P, and ENGEL, W. J. Pheochromocytoma with hypermetabolism — Report of two cases. Ann [illegible]
214 MCGAVACK [illegible]
215 McG [illegible]

Medicine, edited by Cecil, R. L., and Loeb, R. F., W. B Saunders Company, Philadelphia, 1951, 8th edn.
216 McIntyre, D. W. Unilateral chronic pyelonephritis with arterial hypertension — Apparent cure after nephrectomy. J. Urol. (Baltimore), **41**: 900, 1939
217 Mackeith, R. Adrenal sympathetic syndrome chromaffin tissue tumour with paroxysmal hypertension. Brit. Heart J., **6**: 1, 1944
218 McLean, C. R., Fitzgerald, J. D. L., Younghusband, O. Z. and Hamilton, J. D. Diffuse glomerulonephritis induced in rabbits by small intravenous injections of horse serum. Arch. Path. (Chicago), **51**: 1, 1951.
219 McMichael, J Lesions from hexamethonium studies in malignant hypertension. A Ciba Foundation Symposium, Hypertension and neurogenic factors, J & A Churchill Ltd., London, 1954.
220 McQueen, E G "Milk poisoning" and "calcium gout". Lancet, **2**: 67, 1952
220a Mach, R. S, Fabre, J, Duckert, A., Borth, R, and Ducommun, P. Action clinique et métabolique de l'aldostérone (electrocortine) Schweiz med. Wschr., **84**: 407, 1954
221 Maddox, K. Renal dwarfism. Med. J. Aust., **1**: 487, 1932.
222 Maddox, K, Flynn, R., and Day, E. Cushing's Syndrome due to carcinoma of the adrenal cortex. Med J. Aust, **2**: 131, 1949
223 Maher, C. C., and Wosika, P. H. Urologic hypertension — A study of 101 cases J. Urol. (Baltimore), **41**: 893, 1939
224 Maier, H C Intrathoracic pheochromocytoma with hypertension Ann. Surg, **130**. 1059, 1949
225 [illegible] M. The occurren- [illegible] a-
226 Malisoff, S, and Macht, M B Thrombo-angiitic occlusion of the renal artery with resultant hypertension J Urol. (Baltimore), **65**. 371, 1951.
227 Mallory, G. K., Crane, A R, and Edwards, J E Pathology of acute and of healed experimental pyelonephritis. Arch Path. (Chicago), **30**: 330, 1940
228 Mallory, T. B, Castleman, B, and Parris, E. E Case reports of the Massachusetts General Hospital — Case 34502 New Engl J Med., **239**: 933, 1948
229 Manger, W M, Flock, E V, Berkson, J, Bollman, J. L, Roth, G M, Baldes, E J., and Jacobs, M Chemical quantitation of epinephrine and norepinephrine in thirteen patients with pheochromocytoma Circulation (N.Y), **10**. 641, 1954
230 Manners, T Unilateral malignant nephrosclerosis in a child J. Path. Bact., **68**· 63, 1954
231 Mansfield, J S., Mallory, G K., and Ellis, L B The differential diagnosis of chronic Bright's disease — a clinicopathological correlation. New Engl J. Med, *229*. 387, 1943
232 Maring, H, and Freyschmidt, P Hochdruckreaktionen beim Benzodioxantest. Dtsch med. Wschr, **4**. 69, 1953
233 Martensson, J Cardiovascular and renal findings in long-standing diabetes mellitus — A study of 221 patients surviving at least 15 years. Acta med scand, **138**· 94, 1950.
234 Martin, K. W. Spontaneous circumrenal haematoma — A review and report of two cases Brit. med J, **1**· 1118, 1949
235 Master, A. M., Marks, H. H, and Dack, S Hypertension in people over forty, J. Amer. med. Ass, **121**· 1251, 1943.

... Glomerulo Nephritis durch das
236 ... it., 92: 429, 1934.
... ral, renal disease with
237 ... ny. Acta med. scand.,

238 MAYERS, M. R. Lead poisoning in New York State Study of health of 381 lead workers Special Bulletin, New York State Department of Labor, 1928
239 MAYERS, M R Industrial exposure to lead. Occup. Med, 3: 77, 1947.
240 MAYO, C H. Paroxysmal hypertension with tumor of retroperitoneal nerve — Report of a case. J Amer. med. Ass, 89: 1047, 1927.
240a MICHAUD ...
241 MILLER, ... asso...
242 MINNO, A ... Pheochromocytoma — A study of 15 cases diagnosed at autopsy. New Engl J. Med, 251: 959, 1954
243 MOORE, J G Hypertension treated by nephrectomy. J. Urol (Baltimore). 59 297, 1948
244 MORLOCK, C. G., and HORTON, B T. Variations in systolic blood pressure in renal tumor — A study of 491 cases Amer. J. med. Sci, 191: 647, 1936
244a MOULTON ... screening test for ...
245 MOUNTA ... basal metabolic ...
246 ...
infections of the pharynx and tonsils J. med Res, 40. 53, 1919.
247 NESBIT, R M, and RATLIFF, R. K Hypertension associated with unilateral renal disease J Amer med. Ass., 116 194, 1941.
248 NORDMANN, M, and MÜLLER, O Über die Lage eines Blutdruckregulierenden Zentrums in der Medulla Oblongata Klin Wschr, 11: 1371, 1932
249 NYE, L J ... nephrit...
250 OPPENHEIM... with su...
251 PALMER, R ... The renal factor in continued ... nephritis, as revealed b... nephrone- ... J. Med, 223: 165, 1940
252 PARSONS, L Infantilism associated with chronic interstitial nephritis. Brit med J, 2: 481, 1911
253 PASTOR, B H, MYERSON, R. M, WOHL, G T, and ROUSE, P. V. Hypertension associated with renal artery aneurysm and relieved by nephrectomy Ann intern Med ...
253a P...
25...
25... ...MILLAN, R. L Congenital arteriovenous aneurysm of the renal artery. J. Urol, (Baltimore), 58: 235, 1947.
255 PECKHAM, C. H Time of onset and duration of the toxemias of late preg-

nancy in relation to the development of permanent vascular damage. Amer. J. Obstet. Gynec., 42: 638, 1941.
256 PEKKARINEN, A., and PITKANEN, M. Noradrenaline and adrenaline in the urine. Part II. Their excretion in certain normal and pathological conditions. Scand. J. clin. Lab. Invest., 7: 8, 1955.
257 PERERA, G. A. Endocrine factors in hypertension. Bull. N.Y. Acad. Med., 28: 43, 1952.
258 PERERA, G. A. Development of hypertensive manifestations after the disa[illegible]
259 PERERA, [illegible] assoc[illegible] 1952.
260 PETERS, J. P., WAKEMAN, A. M., and LEE, C. Total acid-base equilibrium of plasma in health and disease. X. The acidosis of nephritis J. clin Invest., 6: 517, 1929.
261 PHILIPS, B. Intrathoracic pheochromocytoma Arch. Path. (Chicago), 30 916, 1940
262 PICKERING, G. W. The cerebrospinal fluid pressure in arterial hypertension. Clin. Sci., 1: 397, 1934.
263 PICKERING, G. W. The pathogenesis of malignant hypertension. Circulation (N.Y.), 6: 599, 1952.
264 PICKERING, G. W., and HEPTINSTALL, R. H Nephrectomy and other treatment for hypertension in pyelonephritis Quart J. Med, n s. 22 1, 1953
265 PIETTE, Y., and CORCORAN, A. C. Proteinuria and malignant hypertension Canad. med Ass. J, 71: 542, 1954.
266 PLATT, R. Severe hypertension in young persons — A study of 50 cases, Quart J Med., n s. 17: 83, 1948.
267 PLATT, R., and DAVSON, J. A clinical and pathological study of renal disease Part II. Diseases other than nephritis Quart J. Med, n s 19: 33, 1949.
268 POLLOCK, L J., BOSHES, V, CHOR, H, FINKELMAN, I., ARIEFF, A. J, and BROWN, M. Defects in regulator mechanisms of autonomic function in injuries to spinal cord J. Neurophysiol, 14 85, 1951.
268a POUTASSE, E F, HUMPHRIES, A. W., McCORMACK, L. J., and CORCORAN, A. C Bilateral stenosis of renal arteries and hypertension: Treatment by arterial homografts. J. Amer med Ass, 161: 419, 1956
269 [illegible] ...hilitic occlusion of
270 [illegible] arctation of the aorta. J. Amer med Ass., [illegible]
271 PULASKI, J. E Perineal lymphangioma causing hypertension Ann intern Med., 33. 235, 1950.
272 RAAB, W. Hypertension and tachycardia due to concussion of the brain Amer Heart J., 37: 237, 1949
273 RAAB, W. Hormonal and neurogenic cardiovascular disorders Williams & Wilkins, Baltimore, 1953
274 RAMMELKAMP, C H, Jr., and WEAVER, R S Acute glomerulonephritis — The significance of the variations in the incidence of the disease. J. clin. Invest, 32: 345, 1953.
274a READ, A. E. Malignant hypertension from unilateral tuberculosis kidney treated by nephrectomy. Proc. roy. Soc Med., 49: 119, 1956.
275 REIFENSTEIN, G H., LEVINE, S A, and GROSS, R E. Coarctation of the aorta — A review of 104 autopsied cases of the "adult type", 2 years of age or older Amer. Heart J, 33: 146, 1947

275a REINER, L., KONIKOFF, N., ALTSCHULE, M. D., DAMMIN, G. J., and MERRILL, J. P. Idiopathic paroxysmal myoglobinuria Arch. intern. Med, 97: 537, 1956

276 REIS, R A., and CHALOUPKA, A J. Blood pressure in the newborn following normal and pathological labor. Surg Gynec. Obstet, 37: 206, 1923

277 RICHARDSON, J. E., ROSS, J. H., and TURNBULL, A. L. Reversal of malignant hypertension due to ectopic phaeochromocytoma Lancet, 2: 275, 1955

278 RICHTER, D The inactivation of adrenalin in vivo in man. J. Physiol (Lond), 98 361, 1940

279 RIGGS, T F., and SATTERTHWAITE, R W. Unilateral kidney with partial occlusion of the renal artery associated with hypertension: case report. J Urol. (Baltimore), 45: 613, 1941.

280 RISKIN, A M., SEMERARO, D., and ROBERTAZZI, R W. The control and management of hypertensive crises developing during surgical pro- [illegible]

281 [illegible]

282 ROSCOE, M H Biochemical and haematological changes in Type 1 and Type 2 nephritis Quart. J. Med, n s 19: 161, 1950.

283 ROSENBAUM, M., and MALTBY, G L. Cerebral [illegible] eclampsia A [illegible]

284 ROSENHEIM, M L [illegible] Proc roy S [illegible]

285 ROSENKRANTZ, J. A., and MARSHALL, C. Basal metabolic rate in hypertensive vascular disease Arch. intern Med, 80: 81, 1947.

286 ROTH G M [illegible] RKER, N. W., and PRIESTLEY, [illegible] Report on three siblings with [illegible] 90, 1953

287 RUB [illegible] oloscleresis, hypertension, and cerebral atrophy in an infant. J Pediat, 18. 643, 1941.

288 RUSSI, S., BLUMENTHAL, H T., and GRAY, S. H. Small adenomas of the adrenal cortex in hypertension and diabetes Arch. intern. Med, 76: 284, 1945

289 RYTAND, D A Fatal anuria, the nephrotic syndrome and glomerular nephritis as sequels of the dermatitis of poison oak Amer. J. Med, 5: 548, 1948

290 RYTAND, D A., BURNHAM, DEW K., and COX, A J., Jr. Periarteritis nodosa following the dermatitis of poison oak and of primrose Stanford med Bull, 6 319, 1948.

291 SAHLI Zweites Referat Verh dtsch Kongr inn med., 19. 45, 1901.

292 SALUS, F Zur Frage des bulbären Hochdruckes Klin Wschr., 11: 1542, 1932

293 SALVESEN, H A The blood pressure in idiopathic and symptomatic steatorrhea Acta med scand, 144: 303, 1953

294 SAPIR, O., and BALLINGER, J. Hypertension (Goldblatt) and unilateral malignant nephrosclerosis Arch intern Med, 66 541, 1940

295 SARRE, H Zur Pathogenese und Therapie des nephrotischen Syndroms. Dtsch med Wschr, 79. 1652 and 1713 1954

296 SCHACHT, F. W Hyp[illegible] Arch intern [illegible]

297 SCHROEDER, H A [illegible] Kimpton, Lo[illegible]

298 SCHROEDER, H. A., and FISH, G. W. Studies on "essential" hypertension III. The effect of nephrectomy upon hypertension associated with organic renal disease. Amer. J. med. Sci., 199. 601, 1940

299 SCHUMACHER, G. A., and GUTHRIE, T. C. Studies on headache: mechanism of headache and observations on other effects induced by distention of bladder and rectum in subjects with spinal cord injuries. Arch. Neurol. Psychiat. (Chicago), 65: 568, 1951.

300 SCHWARTZ, N. H., and GROSS, S. Unilateral malignant nephrosclerosis J. Urol (Baltimore), 62: 426, 1949

301 SCOTT, W. W. Blood stream infections in urology — A report of eighty-two cases. J Urol (Baltimore), 21: 527, 1929

302 SEEGAL, D., LYTTLE, J. D., LOEB, E. N., JOST, E. L., and DAVIS, G. On the *exacerbation in chronic glomerulonephritis. J. clin Invest.*, 19: 569, 1940.

303 SHAFFER, B, BURGOON, C F., and GOSMAN, J. H. Acute glomerulonephritis following administration of rhus toxin — Report of a fatal and near fatal case. *J. Amer. med Ass*, *146: 1570, 1951.*

303a SHA'

304 SHE. renal artery with hypertension — case report J Urol. (Baltimore), 59: 302, 1948.

305 SHEARN, M A, and PIROFSKY, B Disseminated lupus erythematous — Analysis of thirty-four cases. Arch. intern Med., 90: 790, 1952

306 SHEEHAN, H. Toxemias of Pregnancy. *J & A. Churchill Ltd*, *London*, 1950 Cited by Dieckmann, W J, "Toxemias of Pregnancy". The C. V Mosby Company, St. Louis, 1952, 2nd edn

307 SHELBURN, S A, BLAIN, D., and O'HARE, J P. The spinal fluid in hypertension J. clin. Invest., 11: 489, 1932

308 SHEPARDSON, H. C, and SHAPIRO, E The diabetes of bearded women — (Suprarenal tumor, diabetes, and hirsutism) — A clinical correlation of the function of the suprarenal cortex in carbohydrate metabolism Endocrinology, *24*: 237, 1939

309 SHIPLEY, A M Paroxysmal hypertension associated with tumor of the suprarenal Ann. Surg., 90: 742, 1929

309a SIMPSON, S A, TAIT, J F, and BUSH, I. E Secretion of a salt-retaining hormone by the mammalian adrenal cortex. Lancet, 2 226, 1952

309b SLOMINSKI-LAWS, M D, KIEFER, J H, and VERMEULEN, C W Arteriovenous aneurysm of the kidney: Case report J Urol (Baltimore), *75: 586, 1956.*

310 SMIRK, F H Observations on the causes of oedema in congestive heart failure Clin Sci., 2: 317, 1936.

311 SMIRK, F. H, and ALSTAD, K S *Treatment of arterial hypertension* by penta- and hexamethonium salts based on 150 tests on hypertensives of varied aetiology and 53 patients treated for periods of two to fourteen months. Brit med. J, 1: 1217, 1951

312 SMITH, G VAN S, and SMITH, O. W Internal secretions and toxemia of late pregnancy. Physiol Rev, 28: 1, 1948

312a SMITH, S. A *Some aspects of lead absorption med J. Aust*, 2: 391, 1925.

313 SMIT ... The effect of

314 SMITHWICK, R H. Surgical treatment of hypertension Amer J. Med., 4: 744, 1948

315 SMITHWICK, R. H, GREER, W. E. R., ROBERTSON, C. W., and WILKINS,

316 with anomalous renal artery — Diagnosis by renal arteriography — Apparent cure after nephrectomy. Pediatrics, 15: 88, 1955.
317 SOBEL, I. P. So-called essential hypertension in childhood Amer. J. Dis. Child, 61: 280, 1941
317a SOWRY, G S C. Phaeochromocytoma: Malignant hypertension Proc. roy. Soc Med, 49. 117, 1956
318 SPALDING, J M. K A case of phaeochromocytoma Brit med. J. I: 564, 1947.
319 SPIEGEL, R. Clinical aspects of periarteritis nodosa Arch intern. Med, 58: 993, 1936.
320 STEINBECK, A W. The plasma volume in glomerulonephritis Clin Sci, 12 327, 1953.
321 STICKNEY, J M, and KEITH, N. M. Renal involvement in disseminated lupus erythematosus Arch. intern Med, 66: 643, 1940
322 SWARM, R. L, and GERMUTH, F. G. Renal lesions in scleroderma. Amer. J. Path, 29: 677, 1953
323 TANQUIST, E J Relationship of pyelonephritis and hypertension and its prognostic outlook. Clin. Med, 59. 1952
324 TAYLOR, H C, Jr Relationship of the hormones to the toxemias of pregnancy. J. Amer med Ass, 120 595, 1942.
325 TAYLOR, R D, CORCORAN, A C, and PAGE, I H Menopausal hypertension — A critical study Amer. J. med. Sci, 213. 475, 1947.
326 TEEL, H M, and REID, D E. A clinical and follow-up study of all cases at Boston Lying-in Hospital over a twenty-year period Amer. J. Obstet. Gynec, 34 12, 1937
327 TELEKY, L A note on blood pressure in lead poisoning. J. industr. Hyg, 19 1, 1937
328 TENNEY, B, Jr., and PARKER, F, Jr The placenta in toxemia of pregnancy Amer J. Obstet Gynec, 39 1000, 1940.
329 THAL, A Selective renal vasospasm and ischemic renal necrosis produced experimentally with staphylococcal toxin — Observations on the pathogenesis of bilateral cortical necrosis Amer. J. Path, 31: 233, 1955
330 THEOBALD, G W. The toxaemias of pregnancy — Experience in Siam and impressions while travelling. Lancet, 1 1030, 1930
331 THOMPSON, C E, and WITHAM, A C. Paroxysmal hypertension in spinal-cord injuries New Engl J Med, 239: 291, 1948.
332 THOMPSON, J E, and SMITHWICK, R H. Human hypertension due to unilateral renal disease with special reference to renal artery lesions Angiology, 3: 493, 1952
333 THOMPSON, R. H S., and TICKNER, A Observations ... oxidase ...
334 THORN, G W ... of the ad... Ann inte...
335 THORN, G W, KOEPF, G F, and CLINTON, M ... ing adrenocortical ...
336 TOBIAN, L ... and es...
337 ... les l'hyper- ... 52, 1946

337a VENNING, E. H., CARBALLEIRA, A., and DRYENFURTH, I. Excretion of sodium-retaining substances J. clin. Endocr., 14: 784, 1954.
338 VOLHARD. Handbuch der Inneren Medizin, 2: 1541, 1931. Julius Springer, Berlin.
339 VOLHARD, F., and FAHR, T. Die Brightsche Nierenkrankheit, Springer, Berlin, 1914. Cited by Pickering, G. W., Circulation (N.Y.), 6. 599, 1952.
340 VON EULER, U. S., FRANKSSON, C., and HELLSTRÖM, J. Adrenaline and noradrenaline output in urine after unilateral and bilateral adrenalectomy in man Acta physiol scand., 31: 1, 1954a.
341 VON EULER, U. S., FRANKSSON, C., and HELLSTRÖM, J. Adrenaline and noradrenaline content of surgically removed suprarenal glands. Acta physiol. scand, 31· 6, 1954b
342 VON EULER, U. S., HELLNER, S., and PURKHOLD, A. Excretion of noradrenaline in urine in hypertension. Scand J clin Lab. Invest, 6 54, 1954
343 VORZIMER, J. J., FISHBERG, A. M, LANGROCK, E G., and RAPPAPORT, E. M The endocrine basis of toxemia of pregnancy. Amer J. Obstet Gynec, 33· 801, 1937.
344 WAALER, E A chromaffine tumour simulating Grave's disease Acta med scand, 123· 1, 1945
345 WAGENER, W. P. Arterioles of the retina in toxemia of pregnancy J Amer. med. Ass., 101: 1380, 1933
346 WAINWRIGHT, J. Hypertension following renal infarction Lancet, 1: 62, 1949
347 WALDENSTRÖM, J. Studien über Porphyrie Acta med. scand, suppl. 82: 3, 1937
348 WALTERS, J H. Hyperpiesis in cardiovascular beri-beri Quart J Med, 22: 195, 1953
349 WALTON, J. N. Phaeochromocytoma of the adrenal. Lancet, 1· 438, 1950
350 WEINREB, M S, SOULES, K. H, and WISSLER, R W Quantitative studies of acute nephrotoxic nephritis in rats Amer J Path, 30· 311, 1954
351 WEINSTEIN, L, and SHELOKOV, A Cardiovascular manifestations in acute poliomyelitis New Engl. J. Med, 244 281, 1951
352 WEISS, S, and PARKER, F, Jr Pyelonephritis. Its relation to vascular lesions and to arterial hypertension Medicine (Baltimore), 18: 221, 1939
353 WELLS A H, and BOMAN, P. G The clinical and pathological identity of pheochromocytoma — Report of a case J. Amer med Ass, 109: 1176, 1937
354 WERTHEIM, A R, LYTTLE, J. D, LOEB, E N, EARLE, D P, Jr, SEEGAL, B C, and SEEGAL, D. The association of type specific hemolytic streptococci with acute glomerulonephritis at the Presbyterian and Babies Hospitals, New York, N.Y, in the years 1936—1942 J clin Invest, 32. 359, 1953
355 WEST, G B., SHEPHERD, D. M, HUNTER, R B, and MACGREGOR, A The function of the organs of Zuckerkandl Clin Sci, 12. 317, 1953
356 WILMERS, M J, CUNLIFFE, A C, and WILLIAMS, R E O Type-12 streptococci associated with acute haemorrhagic nephritis Lancet, 2 17, 1954
357 WILSON, C. Renal factors in the production of hypertension. Lancet, 2: 632, 1953
358 YOUNG, H. H Renal infections associated with prostatic obstruction Bull. Johns Hopk. Hosp, 53: 1, 1933

359 YOUNG, J The eclamptic phenomenon and placental ischaemia J. Obstet Gynaec. Brit. Emp, 50: 221, 1942.
360 YUILE, C. L. Obstructive lesions of the main renal artery in relation to hypertension Amer. J. med. Sci, 207: 394, 1944.
361 ZANGEMEISTER, W. Der Hydrops Gravidarum, sein Verlauf und seine Beziehungen zur Nephropathe und Eklampsie. Z Geburtsh. Gynäk., 81: 491, 1919
362 ZIMMERMAN, H M, and PETERS, J. P. Pathology of pregnancy toxemias J clin Invest, 16 397, 1937

337a VENNING, E. H., CARBALLEIRA, A., and DRYENFURTH, I. Excretion of sodium-retaining substances. J. clin. Endocr., 14: 784, 1954.

338 VOLHARD. Handbuch der Inneren Medizin, 2: 1541, 1931. Julius Springer, Berlin.

339 VOLHARD, F., and FAHR, T. Die Brightsche Nierenkrankheit, Springer, Berlin, 1914. Cited by Pickering, G. W., Circulation (N Y.), 6. 599, 1952.

340 VON EULER, U. S., FRANKSSON, C., and HELLSTRÖM, J. Adrenaline and noradrenaline output in urine after unilateral and bilateral adrenalectomy in man. Acta physiol. scand., 31: 1, 1954a

341 VON EULER, U. S., FRANKSSON, C., and HELLSTRÖM, J. Adrenaline and noradrenaline content of surgically removed suprarenal glands Acta physiol. scand , 31: 6, 1954b

342 VON EULER, U. S., HELLNER, S., and PURKHOLD, A. Excretion of noradrenaline in urine in hypertension. Scand J. clin Lab Invest, 6 54, 1954

343 VORZIMER, J. J., FISHBERG, A M , LANGROCK, E. G , and RAPPAPORT, E. M The endocrine basis of toxemia of pregnancy. Amer. J. Obstet Gynec., 33: 801, 1937.

344 WAALER, E. A chromaffine tumour simulating Grave's disease Acta med. scand., 123. 1, 1945.

345 WAGENER, W. P. Arterioles of the retina in toxemia of pregnancy. J Amer. med. Ass., 101: 1380, 1933.

346 WAINWRIGHT, J. Hypertension following renal infarction Lancet, 1: 62, 1949

347 WALDENSTRÖM, J. Studien über Porphyrie. Acta med scand , suppl 82: 3, 1937

348 WALTERS, J. H Hyperpiesis in cardiovascular beri-beri Quart J Med , 22: 195, 1953.

349 [illegible] Lancet, 1. 438, 1950

350 [illegible] W. Quantitative studies [illegible] J Path , 30: 311, 1954

351 WEINSTEIN, L , and SHELOKOV, A Cardiovascular manifestations in acute poliomyelitis New Engl. J Med , 244. 281, 1951

352 WEISS, S , and PARKER, F , Jr Pyelonephritis. Its relation to vascular lesions and to arterial hypertension Medicine (Baltimore), 18. 221, 1939

353 WELLS A. H , and BOMAN, P. G The clinical and pathological identity of pheochromocytoma — Report of a case J Amer med Ass , 109· 1176, 1937

354 WERTHEIM, A R , LYTTLE, J. D , LOEB, E N , EARLE, D P , Jr , SEEGAL, B C , and SEEGAL, D The association of type specific hemolytic streptococci with acute glomerulonephritis at the Presbyterian and Babies Hospitals, New York, N Y , in the years 1936—1942 J clin Invest., 32· 359, 1953

355 WEST, G B , SHEPHERD, D M , HUNTER, R B , and MACGREGOR, A The function of the organs of Zuckerkandl Clin Sci , 12 317, 1953

356 WILMERS, M J , CUNLIFFE, A C , and WILLIAMS, R E. O Type-12 streptococci associated with acute haemorrhagic nephritis Lancet, 2. 17, 1954

357 WILSON, C. Renal factors in the production of hypertension Lancet, 2 632, 1953

358 YOUNG, H. H Renal infections associated with prostatic obstruction Bull. Johns Hopk. Hosp , 53: 1, 1933

Brunton, 1909; Bickel, 1914; von Monakow, 1920; O'Hare, 1920; [illegible] 1929–30; [illegible] 1931; [illegible] Ayman and Goldshine, [illegible] and Kronfeld, 1932; Schultz, 1932; Ayman and Goldshine, [illegible] and Smirk, 1943a, b; Ehrström, 1945.) Emotional rises of pressure of 10 or 20 mm. are common, and rises of 50 mm. or more are encountered.

Transient pressure increases are exhibited particularly on the first visit in connection with an examination for military service, life assurance, student health survey or clinical examination. That most of these transient rises to near hypertensive levels are due to emotion, tenseness, alertness or some such mental state is highly probable because nearly all subside, sometimes in a few minutes, if the subject can be put at ease (Weitz and Sieben, 1926; Mueller and Brown, 1930; Ayman and Pratt, 1931; Alam and Smirk, 1943a, b; Smirk, 1944; Smirk, 1947, Kilpatrick, 1948).

In many persons the doctor-patient relationship is a potent blood pressure raising stimulus (Ayman, 1930, 1931; Alam and Smirk, 1943a). It is common knowledge that if several blood pressures are taken in succession the level tends to fall. The extent of this fall with habituation varies, but it is often much greater in patients with high than in patients with low blood pressure. Repetition of blood pressure readings at half-minute intervals for between 10 and 15 minutes reduces the blood pressure more than just a few repetitions, provided the patient is given a reassuring explanation of the procedure. Such repetition is an essential for determination of basal blood pressures in patients who are not asleep. It is a deliberate procedure aimed at nullifying the stimulus value of the observer and his sphygomomanometer. Daily visits diminish but do not eliminate the pressor response to medical personnel and sphygmomanometry.

Huber (1933) noted in soldiers that even if repetitions of blood pressure measurements were made at intervals of some weeks or months, the mean (for the group) of the later blood pressure readings was significantly less than the mean pressures for earlier readings. Some further observations from our clinic are reported in Chapter III.

In our experience blood pressures taken by competent technicians are usually lower than blood pressures taken by doctors. We often find that blood pressures taken in a busy outpatient clinic are substantially higher than when they are taken in a quiet side room.

When the blood pressure has been reduced to a steady near-basal level it will usually rise promptly again if the patient is alerted, for example by the entry of a nurse with a tray of instruments (Alam and Smirk, 1943a, Kilpatrick, 1948), or by discussion of illness. When the blood pressure is near to the basal level, rises occur with simple conversation or when the patient's attention is aroused, and this occurs in the absence of conscious emotion or tenseness. Questions or remarks

CHAPTER VII

# PSYCHOSOMATIC ASPECTS OF HIGH BLOOD PRESSURE

Transient blood pressure elevation, which in many instances seems *to be due to tenseness* or *emotion*, is associated *statistically* with an increased expectation of the development of high blood pressure in later life. The tendency to exhibit transient blood pressure rises to overaverage levels might be explained either by a greater degree of tenseness or by a greater degree of reactivity of the circulation to such stimuli. Furthermore, it will be clear, that patients who exhibit transient blood pressure rises may differ from each other in the nature of the physiological or pathological processes which are responsible.

The methods of determining basal blood pressure discussed in Chapter II represent an attempt to discover the level to which the *blood pressure falls under conditions of rest in which* a deliberate attempt is made to reduce physical, metabolic and in particular, mental and emotional activity to a minimal level.

The difference between the casual pressure and the basal pressure may be termed the supplemental pressure. The supplemental pressure represents that part of the casual blood pressure which is due to physical and metabolic activity and to such activities of the mind as emotion, tenseness, alertness or preparedness; it is the source of most of our difficulties in interpreting the significance of casual blood pressure levels.

Many observations have been reported which relate the response of the blood pressure to deliberate provocation by simple stimuli and by more complicated situations such as a stressful interview. A few studies have been made in which the hypertensives or prehypertensives and controls have been grouped into personality types. From the results on such groups a number of interesting generalizations emerged. Finally the detailed psychiatric study of individual case histories has yielded valuable information. Here it is very difficult to make valid generalizations and some examples of case histories are given later.

## TRANSIENT BLOOD PRESSURE INCREASES

Of the blood pressure rises which occur in response to emotion, most are transient, but some are of longer duration (Hensen, 1900;

Brown (1935), and the blood pressure raising reflex from voluntary muscle (Alam and Smirk, 1937) are usually greater in essential hypertension cases than in healthy subjects of the same age group (Alam and Smirk, 1938). Some normotensives however give bigger responses than some hypertensives. The elevations of blood pressure in response to psychical stimuli and in response to cold do not invariably show parallelism (Ruskin et al. 1948).

Not all nervous patients exhibit notable rises of blood pressure at medical interviews According to Hall (1927) most psychoneurotics have low blood pressures, but it seems likely that those of them who do respond to emotional stimuli by blood pressure rises, may be expected to exhibit blood pressure increases more frequently than normal people who are less easily upset. Individuals do not necessarily react to conditions of stress in the same way. As Wolff (1950) said, "There are 'pulse reactors' and 'blood pressure reactors', 'stomach reactors' and 'nose reactors'".

As might be expected, variations in the amount of environmental stress may explain significant differences in the blood pressures when groups of individuals are studied. Stocks and Karn (1924) state that the average blood pressure of children is higher in schools with strict discipline than in those where discipline is lax. Tigerstedt (1926) refers to the higher blood pressures in students in the few weeks before an examination The figures he gives for the systolic blood pressures are surprising; 163 before the written paper and 152 after, 160 before the oral and 149 after; at a later date the blood pressure was 133. Stokvis (1937a) made a similar observation and Funkenstein and Meade (1954) described blood pressure rises averaging 31 mm. Hg systolic in young men waiting to hear the announcement of intern appointments.

Ruskin [illegible]
of some [illegible]
and Cowe[illegible] level of the blood pressure in front-line troops when compared with supporting troops, and somewhat similar results have been reported by others (Gelshtein, 1943; Ehrstrom, 1945) Graham (1945) refers to 695 men aged 20 to 38 whose blood pressures were taken four to eight weeks after battle while in the training area. Most of them had been two to three years in the field and some had had five years in the Middle East. The mean blood pressure was 154/90. There were 187 with diastolic blood pressures exceeding 100 mm Thirty-three of the hypertensives were re-examined after two months' freedom from battle anxieties and the blood pressure level had decreased in 28 of these — their average pressure being 157.7/92.1

Clauss (1923) and Klemperer (1907) showed that in patients under hypnosis appropriate suggestions could raise or lower the blood

likely to provoke emotion cause still larger blood pressure rises in persons who are predisposed. The extent of the blood pressure rise depends not only upon the nature of the stimulus but also on the extent to which the blood pressure has been allowed to fall towards basal before the stimulus is applied.

" Wolf and Wolff (1950) described the effect of deliberately stressful interviews upon the blood pressures of 21 hypertensive and 16 control subjects. The average blood pressures of the 16 normotensive subjects rose from 119/76 to 131/81. The average of the hypertensive group rose from 165/103 to 189/117. Pfeiffer and Wolff (1950) also found that stressful interviews lead to a decrease in the renal blood flow and increase in the filtration fraction in both hypertensive and normotensive individuals; but the increase in renal vascular resistance was definitely greater in the hypertensives. The observations were based on para-amino hippurate and inulin clearances."

Palmer (1950) studied the effect of mental stress on the blood pressure in miscellaneous patients with gastric disorders, nervous fatigue, effort syndrome etc. and found average rises in the systolic pressure of 10 to 15 mm. Hg whereas in essential hypertension the average rise was 21 mm. Hg. The cold pressor test likewise gave greater rises in hypertension than in normotension. He remarked that the patient-doctor situation produced peaks of blood pressure which seemed to be as high as with any of the pressor tests

One may ask whether transient blood pressure rises to near hypertensive levels indicate a physiological response which has taken place in a healthy person, but which is indicative of a predisposition to pathological hypertension, or whether a pathological process is present already which has enhanced the pressor responses to tenseness or emotion. No evidence of which the author is aware points to the existence of any organic pathological process in young subjects exhibiting transient hypertension and which might explain it. It seems more reasonable to regard transient blood pressure elevations in otherwise healthy individuals under the age of 25 as probably representing physiological responses of a larger than average magnitude. These might occur if vasomotor or cardiac reactions to stimuli are excessive or alternatively they might be found in persons whose vasomotor reactions are normal but whose mental reactions to physical stimuli or emotional stress are excessive.

" The question of whether transient blood pressure rises from emotion are due to increases of cardiac output or to vasoconstriction has been debated. Grollman (1929) described increases of cardiac output with emotion and similar results have been obtained by Hickam et al. (1948).

Vasoconstriction in limb vessels has also been demonstrated to occur with emotion and tenseness by Neumann et al. (1942). The reactions to vasomotor reflexes, such as the cold pressor test of Hines and

exhibit these traits to any noteworthy extent. The observation of hundreds of patients, young and old, ignorant and informed, dull and

of hypertension, despite the suggestive evidence advanced by a series of excellent observers."

Weiss et al. (1952) express somewhat similar views: "We have been unable to discover any specific personality conflicts or specific personality structure that seemed related to the hypertension. While evidence of repressed hostility was commonly found, the same thing can be said regarding many other so-called psychosomatic disturbances; and we cannot say from our studies that repressed hostility is any more common in hypertensive patients, or that the nature or degree of its repression differs in hypertensive patients from those with other

Palmer (1950) studied the personalities of 50 patients with essential hypertension. He remarked that originality and special interests and skills seemed to be lacking among his patients but they tended to be

blushing and faintness in 12.

Binger (1945) differs mainly from the above authors in that he refers to the possibility that the origin of hostility may be found in early life and may be basically related to the hypertension. He says of hypertensives: "They are characteristically tense

common feature is an extreme degree of insecurity, with a greatly unsatisfied dependent relationship to a threatening parent." And later: "I do not wish to be understood as stating that this disturbance of character or its ultimate outcome is the cause of hypertension. It is, on the contrary, my suspicion that the psychological disorder and the physiological disorder each represents a different aspect of a more basic disturbance, the nature and cause of which is unknown — though its existence is often foreshadowed early in life."

Saul et al. (1954) study dreams and report: "In our material, hostility seemed present in greater

from the latter. A sixpoint

pressure appreciably. Stokvis (1937b) found that among various suggestions made under hypnosis fear had the most potent blood pressure raising effect. He thought that in predisposed persons chronic fear might be concerned aetiologically in the development of hypertension.

### Comment

It would appear that we are on firm ground in concluding that normotensives and hypertensives usually exhibit some blood pressure rise in response to emotional stimuli or tenseness. The blood pressure rises exhibited by hypertensives are usually much greater. Other stimuli such as the cold pressor test, the blood pressure raising reflex from exercised ischaemic muscle, the Valsalva overshoot, carbon dioxide inhalation and breath holding all induce bigger blood pressure rises in hypertensives (as a class) than in normotensives (as a class). Such evidence would be consistent with the idea that the average degree of reactivity of hypertensives to a variety of stimuli is greater than the average reactivity of normotensives, reactivity being expressed in mm. Hg.

It remains to consider whether there may be evidence also of overaverage discharges of emotion and overaverage tenseness among hypertensive persons.

## THE PERSONALITY CHARACTERISTICS OF HYPERTENSIVE PATIENTS

While differing accounts have been given of the personality characteristics of hypertensive patients, there seems to be almost general agreement that there is need to consider such characteristics as tenseness, neuroticism, hostility, dependent attitudes and conflicts between hostility and dependent attitudes. In the hope of simplifying presentation without distorting the views of authors to be quoted, I have made an arrangement of ideas with some quotations from views expressed by various writers.

### Aggressive Traits

As far back as 1909 Sir Lauder Brunton said about hypertensives. "*Above all things they ought to avoid getting angry.* Emotion, and especially angry emotions, raises the tension very greatly . . ."

Aggressive traits are mentioned alone or in combination with other characteristics by most authors. Som[illegible]

[illegible] hostility in patients with other disorders. Lipkin (1949) for example expressed the following opinion: "One finds similar hostility and dependency in many patients without hypertension. Contrariwise, one finds hypertensives who do not

exhibit these traits to any noteworthy extent. The observation of hundreds of patients, young and old, ignorant and informed, dull and bright, with severe or mild hypertension has failed to convince me that there is any direct causal relationship or indeed, any close cor- [illegible]

Weiss et al. (1952) express somewhat similar views: "We have been unable to discover any specific personality conflicts or specific personality structure that seemed related to the hypertension. While evidence of repressed hostility was commonly found, the same thing can be said regarding many other so-called psychosomatic disturbances; and we cannot say from our studies that repressed hostility is any more common in hypertensive patients, or that the nature or degree of its repression differs in hypertensive patients from those with other psychosomatic disturbances. Weiss et al (1952) recognize, however, a higher incidence of aggressive traits among hypertensives than among the general population.

Palmer (1950) studied the personalities of 50 patients with essential hypertension. He remarked that originality and special interests and skills seemed to be lacking among his patients but they tended to be practical and objective people on the whole independent, efficient and ambitious; and aggressive character traits were common. Of the 50 there was explosive illtemper in 11 and a disposition to vasomotor symptoms such as trembling, blushing and faintness in 12.

Binger (1945) differs mainly from the above authors in that he refers to the possibility that the origin of hostility may be found in early life and may be basically related to the hypertension. He says of hypertensives: "They are characteristically tense individuals given to states of anxiety and depression. Much of their emotional tension can be ascribed to inhibited, but not deeply repressed, aggressive impulses. It is often possible to trace the history of this neurotic development of character to early childhood when the common feature is an extreme degree of insecurity, with a greatly unsatisfied dependent relationship [illegible] be understood [illegible] imate outcome [illegible] suspicion that [illegible] and the physiological disorder each represents a different aspect of a more basic disturbance, the nature and cause of which is unknown — though its existence is often foreshadowed early in life."

Saul et al (1954) study dreams and report: "In our material, hostility seemed present in greater intensity in the manifest dreams of hypertensives than in those of normotens[illegible]

P

scale to measure hostility has been constructed, demarcating three major categories in the intensity of its expression." The authors also recognize that hostility is present to a significant degree in other psychosomatic illnesses.

## Conflict of Aggressive Traits and Dependent Needs

Several psychiatrists have thought that hypertensive patients tended to repress the urge of aggressive impulses because of their desire "to be loved", "to be ingratiating" or "to yield to dependent needs".

Wolf and Wolff (1950) say: "Under a facade often affable and easygoing, they were tense, wary, and suspicious, afraid of committing themselves. They were poised to strike, but withheld their punch with a guilty fear of its consequences." Hambling (1952) says: "It is likely that emotional situations play a great role in the blood-pressure fluctuations of an individual hypertensive, and that a long sustained situation charged with intense, but unexpressed hostility may account for clinical deterioration." He also emphasizes the inability of patients to accept their agressive impulses. "Anger", he says, "is the emotion coming from within that by its destructiveness threatens to break the dependent link with the environment. It is therefore essentially self-destructive and a source of great anxiety. Muscle tension, stiff necks, headaches, palpitations and painful flushings seemed particularly related to this inner battle to prevent the outburst of destructive rage."One feels that arterial hypertension is a somatic expression of this inner rage, and there is good evidence for believing this from the correlations discovered at interview between blood-pressure fluctuations and the emotion of resentment." (Hambling, 1951)."

The conflict between aggressive and dependent needs has been remarked on also by Alexander (1939), and by Gressel et al. (1949), whose work is referred to in more detail later. Matarazzo (1954) goes so far as to say that the suppression of aggressive tendencies in hypertensive persons leads them to show even less overt aggression than normotensives. His inference was based on a study of 40 hypertensives and 40 normotensives in which tasks were to be carried out under the stress of adverse criticism. He points out that the results were also influenced by other factors such as the degree of dependency on the hospital.

## Aggressive Traits of which the Patient is Unaware but which are Inferred from Behaviour or Brought to Light by Analysis or Discussion

Many authors have made passing reference to repression (to subconsciousness) of aggressive impulses, but Menninger (1938) lays

emphasis on this He says: "Patients with hypertension are characterized by an external poise, often gentleness and amiability, beneath which there exists a strong undercurrent of fear which arises from the existence of strongly repressed aggressions, usually dependent upon resentment over threats to the patient's dependent security. To rephrase this rather condensed statement by a paradigm, I would say that hypertension might be expected in a patient whose early childhood was threatened by poverty, death or other disaster whereby he was forced into a premature self-reliance which later shows itself in the form of more or less external (material) success, but accompanied by a constant internal anxiety set up by actual or imagined threats to his security. Upon examination such patients completely deny or reject all suspicion of resentment, hate or fear but describe situations in which such emotions could not but be stimulated. Continued study of such patients often evokes, suddenly and sometimes to the patient's great surprise, frank avowal of such feelings, and then, the real (i.e., the original) reasons for them."

Menninger (1938) also says: "It is very hard, too, to separate the emotional factors stimulated by the physician himself and by the whole program of examination and treatment from those more continuously operative" A somewhat similar remark comes from Lipkin (1949) who points out that the reactions of the patient may differ with the various doctors, the personality of the physician eliciting reactions of hostilities from some patients and of dependency from others.

## Other Personality Traits Attributed to Hypertensive Patients

Other personality traits among hypertensives have been remarked on which might be connected or unconnected with the feelings or with the expression of aggression or dependency or both of these.

Moschcowitz (1919) considers that hypertensive patients tend to be tense, tremendously serious and worried over trifles and that sleep is not restful. He believes they have a limited intellectual horizon. "Ayman (1933) compared the personality of essential hypertension patients with the controls and noted increase in psychomotor activity in the hypertensives. Many of them were dynamic and hyperactive with a large and steady output of energy. They tended to be sensitive and quick tempered."

A high incid[illegible]
and [illegible]
their [illegible] [illegible] between the symptoms experienced by patients with uncomplicated hypertension and with psychoneurosis

Neurotic traits are also emphasized by Morrison and Diehl (1924), Riseman and Weiss (1930), Binger (1945) and Weiss et al. (1952).

## Group Studies with Controls

Intensive psychiatric studies of individual hypertensive patients often yield information of great interest. While valid for the individual studied, such information may not be fully characteristic of the disorder. Hypertensives are an important proportion of the community and we should know the frequency of occurrence of important deviations of personality in hypertensives as compared with controls, even if the psychoanalytical study of large numbers is impracticable. Of value in this connection are certain personality studies with a statistical flavour which aim at a study of the relation between the characteristics of the individual and the level of the blood pressure.

A particularly interesting study comes from Harris, Sokolow, Carpenter, Freedman and Hunt (1953). The authors made a study of "pre-hypertensive" college women with blood pressures exceeding 140 systolic or 90 diastolic or both and in consequence with a good chance actuarially of developing sustained hypertension in later life. They compared these with matched normal controls whose blood pressures were less than 120/90. The subjects of the investigation were unaware of the purposes of the study, and the interviewers and observers did not know which subjects were pre-hypertensives and which were controls until the data had been recorded. It was found that the psychiatrists in the team identified correctly 26 of the 38 cases as being either of the normotensive or hypertensive types and on the basis of personality studies only. This would occur by chance approximately twice in a hundred repetitions. The psychiatrist's judgements were based on the degree of neuroticism and in particular upon the degree of latent hostility, on the break-through of hostility into consciousness under stress and on the degree of anxiety which was aroused when the hostility was perceived. The students were subjected to stressful interviews and their responses were described by two or more staff members who used a list of adjectives to describe the observed reactions The sets of adjectives are set out below.

Adjectives checked significantly more often for the prehypertensives than for the normals by one or two observers

| | | |
|---|---|---|
| aggressive | imprudent | provident |
| awkward | impulsive | prudish |
| blustery | infantile | queer |
| changeable | intense | resentful |
| clever | irritable | restless |
| despondent | loud | self-centered |
| emotional | nagging | sour |
| erratic | nervous | stubborn |
| excitable | noisy | sulky |

fearful
grave
guarded
headstrong
idealistic
obnoxious
opinionated
peculiar
persistent
pessimistic
precise
talkative
temperamental
unsympathetic
unstable
wary

Adjectives checked significantly more often for the normals than for the prehypertensives by one or two observers

adaptable
affected
affectionate
apathetic
appreciative
broad-minded
cautious
conciliatory
conscientious
conservative
considerate
consistent
contented
conventional
co-operative
dependable
easy-going
efficient
even
gentle
humane
kind
liberal
likeable
mannerly
meticulous
peaceable
pleasure-seeking
poised
precise
relaxed
respectful
simple
sociable
sophisticated
sympathetic
tactful
tender
tranquil
trusting
unambitious
witty

The authors remark that among the adjectives which are thought to be more characteristic of pre-hypertensives than of normals there are words conveying opposite meanings, such as headstrong and wary, guarded and impulsive. They explain that pre-hypertensive and hypertensive individuals may exhibit the extremes of over and under-control, being less adaptive than the normotensives. They considered that there was much more social poise and tranquility among the normotensives They showed less tendency to react in an extreme way.

As an additional test the subjects were asked to note down themselves the adjectives which they felt applied in particular to themselves. The marking of the tests by the subjects, who were students, was very similar to the marking by the observers. The pre-hypertensives, for example, applied many more extreme adjectives to themselves than did the normotensives; they were evidently capable of, possibly prone to self criticism.

In a psychiatric interview the "pre-hypertensives responded similarly to patients with clinically diagnosed hypertension, and the personality patterns described were like those noted by the observers during stress." They suggest that "the pre-hypertensives are less well able than normal persons to handle stressful or frustrating situations

(of which the initial college physical examination is one) without becoming emotionally upset, and that therefore *they are more likely* to be subject to the autonomic accompaniments of emotion, including repetitive rises in blood pressure. Such repetitive rises may well be one of the conditions, an important even though perhaps not a necessary or sufficient one, in the network of events leading to fixed hypertension."

Harris (1953) of this same team also made a study of 20 officers with overaverage blood pressures. It was of interest that the high blood pressure group showed in the various stimulus situations a less effective capacity *to compromise between self-assertion and self-effacement in the face of authority. Tact and social awareness were less prominent among this group; they were considered to be less resilient and less flexible.*

Gressel et al. (1949) compared the personality characteristics of 50 consecutive subjects with essential hypertension, 49 subjects chosen *consecutively in a clinic for psychosomatic medicine and 44 subjects* with chronic medical or surgical disorders but unlikely to be associated with a predisposition to psychiatric illness. The personality characteristics chosen for study were impulsiveness, subnormal assertiveness, obsessive-compulsive behaviour, depressive behaviour, anxiety and hysteria. *The presence or absence of such characteristics and the clinical grading thereof were noted. "They found a significant association of hypertension with obsessive-compulsive behaviour and a subnormal assertiveness involving inhibited aggression."* It is of particular interest that they found no significant differences in the rating for neurogenic and *for other types of hypertension (endocrine, renal and mixed).* The report of Binger and his co-workers (1945) also indicates great similarity in the personality patterns of subjects with different types of hypertension. The great importance of this conclusion, should it be sustained, will be referred to later. In the course of discussion of the *paper by Gressel et al. (1949), Dr. Franz Alexander of* Chicago stated that in his opinion there is a causal relationship between a chronic state of inhibited aggressiveness and a chronic state of elevated blood pressure. Dr. George Saslow of St. Louis, in discussion of the same paper, referred to experiments in rats in which two mutually exclusive *impulses — going to food* and being stopped by an air blast — can result in sustained hypertension.

## Time Relationship between Emotional Disturbance and Blood Pressure Elevation

There is no doubt that in essential hypertension patients emotional stimuli almost always raise the blood pressure at the time of their occurrence, and when the emotional difficulties persist the elevation of the blood pressure *may also endure.*

Studies of hypertensive patients have in some instances revealed the beginning of personality disturbance in early life and sometimes blood pressure readings have shown that the emotional disturbance preceded the occurrence of sustained hypertension (Ayman, 1933; Hunt and Sokolow, 1950; Weiss et al., 1952). On the other hand, in some instances the personality disturbance seemed to be of recent origin (Ayman, 1933). Our own experience corresponds with that of Ayman In some instances personality difficulties have been of long duration, almost certainly longer than the hypertension; in others hypertension preceded the emotional difficulties.

### Effects of Treatment as Evidence of the Importance of Psychosomatic Factors in High Blood Pressure Patients

Though very few patients exhibit normal blood pressures even after the most extensive psychotherapy (Weiss, 1953), there seems to be little doubt that symptoms may be much relieved when patients are helped with their personal problems (Weiss, 1953). Our own experience is in entire accord with this

Hunt and Sokolow (1950) pointed out the possibility that some of the improvements in hypertensives might be due to the development of grateful and dependent attitudes. Binger (1945) thought it was helpful to encourage hypertensives to work off their aggression by moderate physical exercise and by directed work.

Ayman and Pratt (1931) made the experiment of administering a placebo. They said "In this study it was found that in 82 per cent definite symptomatic relief was obtained in a group of forty patients treated by simple suggestion, which consisted of prescribing a few drops of dilute hydrochloric acid daily. This impressively tasting medicine, undoubtedly nonspecific, coupled with continual encouragement, was used over periods of from one week to four months with a resultant success in 82 per cent." Ayman (1931) also encountered "side effects" from his placebo We have also had this experience in our clinic. Patients who were given placebos (injections of distilled water) and apparently thought they were having methonium compounds, not infrequently complained of dry mouth and inability to read the newspaper because of blurred vision.

In our experience the relief of hypertension by the effective use of hypotensive agents has been associated in most patients with great relief of emotional tension, exceeding the effects of placebos. Although some patients have not been relieved, the majority have, and their individual histories and the persistence of improvement with continuing treatment make it difficult to avoid the conclusion that this is something more than a chance association. The relief has involved decrease in aggression and lessening of emotional tension in the sense that they are much less disturbed by children's noise, banging

doors, visits from strangers, telegrams, telephones and exciting films. They are less apt to speak angrily and less apt to bottle their rage. Such relief has occurred in patients who had very high blood pressures but no definite symptom other than a state of tension, with or without aggressive traits. Nearly all such patients have told me that treatment was well worth while for the relief afforded irrespective of hypertension or other considerations.

One patient was of particular interest. She suffered from glomerulonephritis and was followed for a period of approximately fifteen years. In the early stages her blood pressure was only moderately elevated. She maintained comparatively good health, was a talented singer and made public appearances with surprisingly little tenseness or emotion on appearing before an audience. Latterly she reappeared with a very high blood pressure, grade III retinal changes with a certain amount of dyspnoea. She gave a history that for some years she had noticed an increasing tenseness and had lost her customary imperturbability before an audience. Treated with methonium compounds she responded very well and the blood pressure was much reduced, the breathlessness disappeared and she informed us that once again the feeling of tenseness had gone.

Another hypertensive patient (female, married, aged 37) was, when first seen, one of the most difficult of patients and a trouble maker. Three separate doctors had tried to unload her on to our clinic. I was concerned lest she should upset other patients. It is scarcely an exaggeration to say she dripped venom. She was a severe grade 3 hypertensive and somewhat unwillingly she was accepted for treatment. Her blood pressure was reduced by hexamethonium; she had more than usual trouble with side effects and was given a lot of attention for this. No overt psychotherapy was given, in fact the patient was scarcely sufficiently approachable to make possible an adequate history. Her personality changed, overt vituperation gave place to rather witty thrusts about the side effects of methonium salts, injections and the like. Within a few months she became cheerful and approachable and she was willing to speak frankly about her change in attitude, of which she was fully aware. She had been full of boiling anger, irritation and resentment which could be aroused on very slight or no provocation. On the occasion of a minor annoyance she threw a knife at her husband (and hit him). Coincidentally with decrease of blood pressure and sympathetic blockade she seemed to have lost her disposition to anger. Referring to an event which would have justified some vexation she said "I wanted to be angry but I couldn't — I just had to laugh" The improvement in personality was evident in her family setting and persisted up to the time of her death about 18 months later This case was exceptional but decrease of aggression of a less marked degree was of frequent occurrence.

## THE BLOOD PRESSURE IN PSYCHOTIC PATIENTS

Mueller (1922) reported that the blood pressure was raised in melancholia and subsided if this improved. He found a close relationship between emotions and the level of the blood pressure. Guirdham (1950) also found the blood pressure raised in states of depression and considers that it remains so until the illness is cured. In cases treated by convulsive therapy the blood pressure ordinarily returns to normal at the end of treatment. In the manic phase of manic depressive psychosis the blood pressure was usually, but not invariably, low. Parkin (1927) and Paddle (1928), however, found little difference between the blood pressures in melancholia and mania.

There are several papers referring to the comparatively low level of the blood pressure in schizophrenia. Lingjaerde et al. (1949) state that of 122 schizophrenic women under the age of 40, 60 per cent had a systolic blood pressure of 100 mm. or less. Below the age of 60 there were fewer hypertensives than would be expected from the statistics of Master et al. but above the age of 70 there was a usual incidence of hypertension. The authors remark that the younger schizophrenics were in the active phase of the disease, the older patients were in an inactive phase. Freeman et al. (1932) report that in schizophrenia the mean systolic blood pressure was 11.2 mm. lower than a series of normal controls and that the diastolic pressure was 16.7 mm. below their controls. Between 40 and 60 years of age the majority of their patients had blood pressures under 130/75. The body build in schizophrenics is usually of the linear rather than the lateral type and this may in part explain the lower blood pressure levels. Earle and Earle (1955) report that the responses to the cold pressor test are reduced in schizophrenics as compared with normal controls. According to Paddle (1928) blood pressures tend to be lower in epileptics.

Darrow and Solomon (1934) studied galvanic skin reflexes and blood pressure changes in psychotic states. They noted [illegible] blood pres[illegible] poor ins[illegible] 193 psy[illegible] significant correlation between elevated blood pressure and repressed hostile emotion.

Greenblatt et al. (1947) found that lobotomy caused blood pressure falls in normotensives and, to a greater extent, in hypertensives. Seven out of the eight hypertensives had returned almost to the original high level in 1 to 5 months after operation.

The effect on the blood pressure of ephedrine hydrochloride injections (30 mg. intravenously) was studied in manic depressives schizophrenics and normals by [illegible] blood [illegible]

[illegible]

doors, visits from strangers, telegrams, telephones and exciting films. They are less apt to speak angrily and less apt to bottle their rage. Such relief has occurred in patients who had very high blood pressures but no definite symptom other than a state of tension, with or without aggressive traits. Nearly all such patients have told me that treatment was well worth while for the relief afforded irrespective of hypertension or other considerations.

One patient was of particular interest. She suffered from glomerulonephritis and was followed for a period of approximately fifteen years. In the early stages her blood pressure was only moderately elevated. She maintained comparatively good health, was a talented singer and made public appearances with surprisingly little tenseness or emotion on appearing before an audience. Latterly she reappeared with a very high blood pressure, grade III retinal changes with a certain amount of dyspnoea. She gave a history that for some years she had noticed an increasing tenseness and had lost her customary imperturbability before an audience. Treated with methonium compounds she responded very well and the blood pressure was much reduced, the breathlessness disappeared and she informed us that once again the feeling of tenseness had gone.

Another hypertensive patient (female, married, aged 37) was, when first seen, one of the most difficult of patients and a trouble maker. Three separate doctors had tried to unload her on to our clinic. I was concerned lest she should upset other patients. It is scarcely an exaggeration to say she dripped venom. She was a severe grade 3 hypertensive and somewhat unwillingly she was accepted for treatment. Her blood pressure was reduced by hexamethonium; she had more than usual trouble with side effects and was given a lot of attention for this. No overt psychotherapy was given, in fact the patient was scarcely sufficiently approachable to make possible an adequate history. Her personality changed, overt vituperation gave place to rather witty thrusts about the side effects of methonium salts, injections and the like. Within a few months she became cheerful and approachable and she was willing to speak frankly about her change in attitude, of which she was fully aware. She had been full of boiling anger, irritation and resentment which could be aroused on very slight or no provocation. On the occasion of a minor annoyance she threw a knife at her husband (and hit him). Coincidentally with decrease of blood pressure and sympathetic blockade she seemed to have lost her disposition to anger. Referring to an event which would have justified some vexation she said "I wanted to be angry but I couldn't — I just had to laugh." The improvement in personality was evident in her family setting and persisted up to the time of her death about 18 months later. This case was exceptional but decrease of aggression of a less marked degree was of frequent occurrence.

in hypertensives than in normotensives, but as there is evidence of increased vascular reactivity in hypertension, it would be unsafe to use the magnitude of the pressor response to tenseness and emotion as evidence that it is the psychological reactions that are excessive in hypertensives. *Attempts to compare the psychological reactions of hypertensives and normotensives are best made by study of mental processes.*

Psychiatrists and physicians interested in hypertension have been impressed, however, by the amount of psychiatric abnormality which they discovered among their patients and we have had in our clinic evidence that the association between high blood pressure and certain forms of psychopathology is not fortuitous. Yet the relationship between psychopathology and hypertension can be exaggerated especially in hospital or in consulting practice. Several workers in their studies of patient psychology eliminated those who had had strokes or congestive heart failure or other indications of organic damage induced by high blood pressure. Most patients sent to hospital have some complaint or discomfort. If the method of selecting patients for study is one which gives a preference to patients with symptoms but no manifest organic disease it is likely to include many with psychoneurosis. It is well known among psychiatrists that many patients with psychoneurotic manifestations exhibit aggression, sometimes manifest, sometimes repressed, and [illegible]
et al., 1952) Furtherm[illegible]

[illegible] proportion of hypertensives who are handicapped to a greater or lesser degree by such psychiatric difficulties and in some patients feelings of stress and boiling anger are recognized as the main and sometimes the only symptoms. In some instances the continued discomfort of manifestations such as headache and dizziness have no doubt aggravated this disposition.

We have had great interest in the group of patients who recognize in themselves the symptoms of irritability, tenseness and unwarranted anger and resentment. We find that in the definite majority of them, effective blood pressure reduction by methonium compounds has led to an important lessening of emotional tension, to a greater feeling of relaxation and to a much reduced tendency to irritation and to decrease in manifestations of aggression. Th[illegible]

[illegible]
particularly [illegible]
high but wh[illegible]
tension apart [illegible]

## COMMENT

It seems that the blood pressure level varies in the psychoses being for example, lower in schizophrenia. There seems to be a scope for more detailed study.

It is generally accepted that normotensives and hypertensives usually exhibit blood pressure elevations in response to a variety of stimuli which induce mental activity, tenseness, alertness or emotion. Most authors would agree that the elevations of blood pressure in response to psychic stimuli are more pronounced in the hypertensives, but attempts at explaining this encounter some difficulties. The classification of people into hypertensives and non-hypertensives is largely in terms of casual blood pressures. Consequently those who either have strong emotions or alternatively who have strong reactions of their circulatory system to normal emotions, or who have some combination thereof, are more likely to exhibit higher levels of blood pressure and are therefore more likely to be classified as hypertensive. To some extent at least the means of determining whether a person should be classified as hypertensive or not predetermines that a number of individuals with overstrong emotional reactions or tenseness as well as individuals with strong circulatory reactions to normal emotion will be included in the category of hypertensives.

The medical literature abounds with examples of large blood pressure rises which have occurred in response to deliberate or to inadvertent psychical stimulation. In most of the writings the tendency has been to attribute these blood pressure increases to an excess of tenseness or emotion, but the alternative explanation referred to earlier deserves consideration, namely, that as the result of changes in the vascular system a normal emotional response is accompanied by an excessive cardiovascular response.

There is good evidence that most hypertensives react excessively to a great variety of pressor stimuli. Examples of excessive reactions to stimuli acting through the nervous system are seen in the responses to the cold pressor reflex (Hines and Brown, 1935) to the blood pressure raising reflex from muscles (Alam and Smirk, 1938), to the Valsalva overshoot (Finnerty and Freis, 1950). The pressor responses to chemical stimulation are also exaggerated in hypertension, for example the blood pressure raising action of carbon dioxide inhalation (Raab, 1953), the breath holding test (Ayman and Goldshine, 1939) and, when the blood pressure control mechanism is blocked by hexamethonium, the pressor responses to noradrenaline, angiotonin and to S-methyl *iso*-thiourea are all much greater in hypertensives than in normotensives (Black and Doyle, 1953; Doyle and Black, 1955) Such results make it likely that the pressor effects of normal degrees of tenseness and emotion will be greater in hypertensives than in normotensives.

We know emotional stimuli usually cause larger blood pressure rises

The observations of O'Hare (1920) are of considerable interest. He noted for example that if exciting noises occurred near the patient the pressure often rose to a surprising degree. He found that talking about the high blood pressure was often a sufficient stimulus to induce a blood pressure elevation. Discussions about blood pressure and operations seem to be especially potent stimuli but odd items appear, such as thinking about a dead pet cat. O'Hare (1920) also noted much larger rises in blood pressure from exercise in hypertensive than in normotensive patients. He also observed that many patients with elevated blood pressure exhibited a rise of blood pressure following the administration of nitroglycerin.

Ayman (1930/1931) also refers to an important change in blood pressure level associated with a change of doctor. In our experience the telephone bell going unanswered, a patient nearby who is ill and distressed, disturbing noises from an adjacent ward, the noise of a patient who slips down and falls in the corridor outside, reference to a sister who died from high blood pressure, and many similar situations or topics have given rise to blood pressure elevations which would appear to be of emotional origin and which did not seem to involve anger or resentment. It would, of course, be possible to imagine that in individual cases resentment was in some way bound up with many of the examples which I have quoted, but unless we are to extend considerably the limits of what can be fairly brought under the heading of resentment or suppressed anger, it seems unlikely that the examples given have evoked blood pressure rises through this mechanism.

In a recent paper, Hambling[38] gives a number of excellent examples of the relationship between the blood pressure level and topics of conversations at psychosomatic interviews. There is very little doubt that a person with hypertension, exposed to an emotional conversation will usually respond by considerable increases of blood pressure. It should, however, be borne in mind in [illegible]
tensive responds also to a great [illegible]
blood pressure increases. Therefore [illegible]

[illegible] overaverage intensity in hypertensive patients. That they are of overaverage intensity and [illegible]
considerable [illegible]
and ver [illegible]
to the [illegible] as do other stimuli.

## References

1 ALAM, G M, and SMIRK, F H. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles J Physiol (Lond.), 89, 372, 1937

corresponding improvement in personality has been encountered but the interpretation of this is more difficult as there have been other improvements such as decrease in headache, in dizziness, in breathlessness, or anginal pain.

We have often enquired as to the duration of the personality characteristics so often attributed to hypertension. In some instances these have seemed to have been of comparatively recent origin, in others they have been of long duration but exaggerated recently, sometimes they have been of long duration more or less unchanged up to the time of starting treatment.

Our experiences are such that we can say with no hesitation that many patients give definite histories of tenseness and aggressive impulses sometimes with and sometimes without corresponding anxiety. A large proportion of these get considerable or complete relief from such manifestations when the blood pressure is reduced by methonium salts and this occurs without overt psychotherapy. Our experience now extends over a period of seven years. Recurrence of their symptoms is so unusual that one is inclined to feel that the blood pressure level itself or some physiological phenomenon related to it may have played some part in raising the "emotional tone" to an abnormal level. The recently described central nervous component in the action of hexamethonium (Chapter XVIII) may perhaps be part of the explanation.

It is quite clear that increases in "emotional tone", like many other stimuli, have a greater effect on the blood pressure in hypertension than they have in health. In so far as blood pressure elevation as such leads on to various symptomatologies it is to be expected that increases of "emotional tone" will cause increase in symptoms not only directly by effects upon the higher centres but also by the intermediation of blood pressure increase. It is to be expected that objective manifestations will also result sometimes from the effects of emotion.

The conflict between aggressive trends and dependent needs has been commented on by many writers. It is of interest, therefore, to record our impressions from a clinic concerned very largely with hypotensive treatment. We have used mostly methonium compounds but in about 70 patients, treatment with veratrum alkaloids has been instituted. The friendliness and good relations at this clinic have always been a source of gratification to the doctors who have worked in it. This has persisted even though many patients on veratrum have been rendered most uncomfortable. Manifestations of aggression in its more obvious as well as its less obvious forms have been conspicuously lacking. At the same time we have on a number of occasions been conscious of, or have had brought to our notice, patients who, while outwardly pleasant and controlled, have been a source of anxiety to their families.

24 EHRSTRÖM M C. Psychogene Blutdruckssteigerung Acta med scand, 122. 546, 1945.

25 FAHRENKAMP, K Die psycho-physischen Wechselwirkungen bei den Hypertonieerkrankungen. Eine klinische Studie über die praktische Bedeutung der Blutdruckkurve Stuttgart, Hippokrates-Verlag, p. 143, 1926 Cited by Dunbar, F., "Emotions and bodily changes", Columbia University Press, New York, 1935

26 FINNERTY, F. A, Jr, and FREIS, E. D Experimental and clinical evaluation in man of hexamethonium ($C_6$), a new ganglionic blocking agent. Circulation (N Y), 2 828, 1950

27 FRASER, J., and COWELL, E. M Clinical study of blood pressure in wound conditions. J. Amer. med. Ass., 70: 520, 1918

28 FREEMAN, H, HOSKINS, R G, and SLEEPER, F. H. The blood pressure in schizophrenia Arch Neurol Psychiat (Chicago), 27: 333, 1932

29 FUNKENSTEIN, D H, and MEADE, L. W. Nor-epinephrine-like and epinephrine-like substances and the elevation of blood pressure during acute distress J. nerv. ment Dis, 119. 380, 1954

30 GELSHTEIN, E. M. Clinical characteristics of hypertensive disease under war conditions Klin Med (Wien), 21· 10, 1943 Cited by Ruskin, A., Amer. Rev Soviet Med, 3. 260, 1946

31 GRAHAM, J D P High blood pressure after battle. Lancet, 1· 239, 1945

32 GREENBLATT, M, ARNOT, R E, POPPEN, J. L, and CHAPMAN, W. P. Report on lobotomy studies at the Boston Psychopathic Hospital Amer. J. Psychiat., 104· 361, 1947.

33 GRESSEL, G C, SHOBE, F. O, SASLOW, G., DUBOIS, P. H., and SCHROEDER, H A Personality factors in arterial hypertension J Amer. med. Ass., 140. 265, 1949

34 GRO[illegible]

35 GUIRDHAM, A Some new concepts of blood pressure. Med Press, p. 344, 1950

36 HALL, S B Blood pressure in psychoneurosis Lancet, 2: 540, 1927

37 HAMBLING, J Emotions and symptoms in essential hypertension Brit. J. med Psychol, 24· 242, 1951.

38 HAMBLING, J Psychosomatic aspects of arterial hypertension Brit. J. med. Psychol, 25 39, 1952

39 HARRIS R E [illegible] an[illegible] Re[illegible] Re[illegible] [illegible], Berkeley, 1953

40 HARRIS, R E, SOKOLOW, M, CARPENTER, L G, FREEDMAN, M, and HUNT, S P Response to psychologic stress in persons who are potentially hypertensive Circulation (N Y), 7· 874, 1953.

41 HENSEN, H Beitrage zur Physiologogie und Pathologie des Blutdrucks Dtsch Arch klin Med, 67: 436, 1900

42 HICKAM, J B, CARGILL, W H, and GOLDEN, A Cardiovascular reactions to emotional stimuli. Effect on the cardiac output, arteriovenous oxygen difference, arterial pressure, and peripheral resistance. J. clin Invest, 27 290, 1948

43 HINES, E A, and BROWN, G E The hereditary factor in the reaction of blood pressure to a standard stimulus (cold): preliminary report. Proc Mayo Clin, 10 371, 1935

2 ALAM, G. M., and SMIRK, F. H. Blood pressure raising reflexes in health, essential hypertension, and renal hypertension Clin. Sci., 3: 259, 1938.

3 ALAM, G. M., and SMIRK, F. H. Casual and basal blood pressures. I. In British and Egyptian men. Brit. Heart J., 5: 152, 1943a

4 ALAM, G. M., and SMIRK, F. H. Casual and basal blood pressures II. In essential hypertension. Brit. Heart J., 5: 156, 1943b.

5 ALEXANDER, F. Emotional factors in essential hypertension Psychosom. Med., 1: 173, 1939.

6 ALKAN, L [illegible] krates-[illegible] and bc [illegible]

7 APPEL, K. [illegible] reactions in the psychoses. Arch. Neurol. Psychiat. (Chicago), 27: 159, 1932.

8 AYMAN, D. Normal blood pressure in essential hypertension J. Amer. med. Ass., 94: 1214, 1930

9 AYMAN, D. An evaluation of therapeutic results in essential hypertension. II. The interpretation of blood pressure reductions. J Amer. med. Ass, 96: 2091, 1931.

10 AYMAN, D. The personality type of patients with arteriolar essential hypertension Amer. J med Sci., 186: 213, 1933.

11 AYMAN, D, and GOLDSHINE, A. D. The breath holding test. Arch. intern Med., 63: 899, 1939.

12 AYMAN, D., and GOLDSHINE, A. D. Blood pressure determinations by patients with essential hypertension I The difference between clinic and home readings before treatment. Amer J med. Sci, 200, 465, 1940

13 AYMAN, D, and PRATT, J. H. Nature of the symptoms associated with essential hypertension. Arch. intern Med, 47: 675, 1931

14 BICKEL, H. Über die normale und pathologische Reaktion des Blutkreislaufs auf psychische Vorgänge Neurol Zbl, 33. 90, 1914.

15 BINGER, C A critique of psychotherapy in arterial hypertension Bull N.Y Acad Med, 21: 610, 1945

16 BINGER, C. A L, ACKERMAN, N. W., COHN, A. E, SCHROEDER, H S, and STEELE, J. M Personality in arterial hypertension, psychosomatic medicine monographs. American Society for Research in Psychosomatic Problems, New York, 1945.

17 BLA [illegible]

18 BROWN, G E. Daily and monthly rhythm in the blood pressure of a man with hypertension: a three-year study Ann intern Med., 3: 1177, 1929—30

19 BRUNTON, L. Blood pressure in man: Its estimation and indications for treatment. Brit. med. J, 2: 64, 1909.

20 CLAUSS, O. Blutdruckmessung als psychisches Trauma Münch med Wschr., 70. 741, 1923

21 DAR [illegible] A. P. Galvanic skin reflex and blood pressure [illegible] sensory, indifferent, idea- [illegible] Neurol Psychiat. (Chicago), 32: 273, 1934

22 DOYLE, A. E., and BLACK, H. Reactivity to pressor agents in hypertension. Circulation (N Y), 12. 974, 1955

23 EARLE, A., and EARLE, B V. The blood pressure response to pain and emotion in schizophrenia. J nerv ment. Dis., 121: 132, 1955.

24 EHRSTRÖM M. C. Psychogene Blutdruckssteigerung. Acta med scand, 122. 546, 1945.
25 FAHRENKAMP, K Die psycho-physischen Wechselwirkungen bei den Hypertonieerkrankungen. Eine klinische Studie über die praktische Bedeutung der Blutdruckkurve Stuttgart, Hippokrates-Verlag, p. 143. 1926 Cited by Dunbar, F., "Emotions and bodily changes", Columbia University Press, New York, 1935
26 FINNERTY, F A, Jr., and FREIS, E D Experimental and clinical evaluation in man of hexamethonium ($C_6$), a new ganglionic blocking agent. Circulation (N Y), 2 828, 1950.
27 FRASER, J., and COWELL, E M Clinical study of blood pressure in wound conditions J Amer. med Ass, 70: 520, 1918
28 FREEMAN, H, HOSKINS, R. G, and SLEEPER, F H The blood pressure in schizophrenia Arch Neurol Psychiat (Chicago), 27: 333, 1932
29 FUNKENSTEIN, D H, and MEADE, L. W Nor-epinephrine-like and epinephrine-like substances and the elevation of blood pressure during acute distress J nerv ment. Dis, 119 380, 1954
30 GELSHTEIN, E M Clinical characteristics of hypertensive disease under war conditions Klin Med (Wien), 21 · 10, 1943 Cited by Ruskin, A., Amer Rev Soviet Med., 3, 260, 1946
31 GRAHAM, J D P High blood pressure after battle. Lancet, 1: 239, 1945
32 GREENBLATT, M, ARNOT, R E, POPPEN, J. L, and CHAPMAN, W. P. Report on lobotomy studies at the Boston Psychopathic Hospital Amer. J Psychiat, 104 361, 1947
33 GRESSEL, G C, SHOBE, F O, SASLOW, G, DUBOIS, P. H., and SCHROEDER, H A Personality factors in arterial hypertension J Amer. med. Ass., 140 265, 1949
34 GROLLMAN, A Physiological variations in the cardiac output of man. IV. The effect of psychic disturbances on the cardiac output, pulse, blood pressure and oxygen consumption of man Amer J Physiol, 89: 584, 1929
35 GUIRDHAM, A Some new concepts of blood pressure. Med. Press, p. 344, 1950
36 HALL, S B Blood pressure in psychoneurosis Lancet, 2 540, 1927
37 HAMBLING, J Emotions and symptoms in essential hypertension Brit J. med Psychol, 24 242, 1951
38 HAMBLING, J Psychosomatic aspects of arterial hypertension Brit J med Psychol, 25 39, 1952
39 HARRIS, R E Dominance [illegible] and low blood pre[illegible] Research Memoranc[illegible] Research, Universit[illegible]
40 HARRIS, R E [illegible] S P [illegible] hyper[illegible] 1953
41 HENSEN, H Beiträge zur Physiologie und Pathologie des Blutdrucks Dtsch Arch klin Med, 67 436, 1900
42 HICKAM, J B, CARGILL, W. H., and GOLDEN, A Cardiovascular reactions to emotional stimuli: Effect on the cardiac output, arteriovenous oxygen difference, arterial pressure, and peripheral resistance J clin Invest, 27 290, 1948
43 HINES, E A, and BROWN, G E. The hereditary factor in the reaction of blood pressure to a standard stimulus (cold). preliminary report Proc. Mayo Clin, 10 371, 1935

44 HOUSTON, W. R. The spasmogenic aptitude. Med. Clin. N. Amer., *12:* 1285, 1929.

45 HUBER, E. G. Systolic and diastolic blood pressure in healthy men Hum. Biol., 5: 541, 1933.

46 HUNT, S. P., and SOKOLOW, M. The person with essential hypertension (dynamic psychological factors in the disease). Amer. J. Med., *8:* 537, 1950.

47 KILPATRICK, J. A The variation of casual, basal, and supplemental blood pressures in health and in essential hypertension. Brit. Heart J., 10: 48, 1948

48 KLEMPERER, F. Blutdruck und Pulsdruckuntersuchungen bei Gesunden und Kranken. Verhandl. d. Kongr. f. inn. Med, 34: 398, 1907.

49 KRONFELD, A. Kreislaufneurosen bezw. Herzneurosen vom Standpunkt des Psychotherapeuten. In: Herzneurosen und Moderne Kreislauftherapie, Dresden und Leipzig, Steinkopff. p. 18, 1932. Cited by Dunbar, F., "Emotions and bodily changes", Columbia University Press, New York 1935

50 LIAN, C. Variations de la tension artérielle moyenne dans les efforts et les émotions C. R. Soc Biol (Paris), 107: 1113, 1931.

51 LINGJAERDE, O., LAANE, C L., and STRÖM, H The variation of blood pressure with age in schizophrenics. Acta psychiat. (Kbh) Supplem. 60: 133, 1949.

52 LIPKIN, M. Psychosomatic factors in essential hypertension Med. Clin N. Amer., 33: 703, 1949.

53 MATARAZZO, J. D. An experimental study of aggression in the hypertensive patient. J. Personality, 22: 423, 1954.

54 MENNINGER, K A Emotional factors in hypertension Bull N Y. Acad. Med., 14: 198, 1938.

55 MILLER, M. L Blood pressure findings in relation to inhibited agressions in psychotics. Psychosom Med, 1. 162, 1939.

56 MORRISON, A. W, and DIEHL, H S Some studies on mental hygiene needs of freshmen university students (preliminary report) J. Amer med Ass, 83. 1666, 1924

57 MOSCHCOWITZ, E. Hypertension. its significance, relation to arteriosclerosis, and nephritis, and etiology. Amer. J med Sci., 158: 668, 1919

58 MUELLER Die Kapillaren der menschlichen Koeperflaeche Stuttgart, p. 118, 1922. Cited Alam, G. M, and Smirk, F H, Brit Heart J., 5 156, 1943

59 MUELLER, S C, and BROWN, G E. Hourly rhythms in blood pressure in persons with normal and elevated pressures Ann intern Med., 3. 1190, 1930.

60 NEUMANN, C, COHN, A E., and BURCH, G E A study of the influence of the character of an examining room on the peripheral blood vessels of normal, hypertensive, and senile subjects J clin Invest., 21 651, 1942

61 O'HARE, J. P Vascular reactions in vascular hypertension Amer. J med Sci, 159 369, 1920.

62 PADDLE, K. C. L. A review of blood-pressures in the insane J. ment. Sci, 74: 733, 1928

63 PALMER, R S Psyche and blood pressure — 100 mental stress tests and 50 personality surveys in patients with essential hypertension J Amer. med. Ass, 144: 295, 1950

64 PARKIN, G G. Some observations on the study of the blood-pressure in the insane. J. ment. Sci, 73: 240, 1927

65 PFEIFFER, J B., and WOLFF, H G Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects

with and without essential hypertension; observations on the rôle of neural activity in regulation of renal blood flow. J. clin. Invest., 29: 1227, 1950.

66 RAAB, W Hormonal and neurogenic cardiovascular disorders Williams & Wilkens Co, Baltimore, p. 268, 1953

67 RISEMAN, J E. F., and WEISS, S. The symptomatology of arterial hypertension. Amer. J. med. Sci., 180: 47, 1930

68 RUSKIN, A., BEARD, O W., and SCHAFFER, R. L. "Blast hypertension" — elevated arterial pressures in the victims of the Texas City disaster. Amer J Med, 4: 228, 1948

69 SAUL, L., SHEPPARD, E., SELBY, D., LHAMON, W., SACHS, D., and MASTER, R. The qualification of hostility in dreams with reference to essential hypertension Science, 119: 382, 1954

70 SCHULTZ [illegible]
Thi[illegible]
bod[illegible]

71 SMIRK, F. H Casual and basal blood pressures IV. Their relationship to the supplemental pressure with a note on statistical implications. Brit. Heart J., 6: 176, 1944

72 SMIRK, F H Some observations on high blood pressure N. Z. med. J., 46: 85, 1947

73 STIEGLITZ, E J Emotional hypertension Amer. J. med Sci., 179, 775, 1930

74 STOCKS, P., and KARN, M. N Blood pressure in early life — A statistical study Cambridge University Press, Cambridge, 1924

75 STOKVIS, B Blutdruckregistrierung als Methodik zur psychophysischen Forschung Psychiat neurol. Bl (Amst.), 41: 380, 1937a.

76 STOKVIS, B Étude de l'influence de l'hypnose sur la pression du sang, à l'aide d'une nouvelle méthode d'enregistrement automatique ininterrompu J. Physiol Path. gén., 35: 691, 1937b.

77 TIGERSTEDT, C Der Blutdruck des Menschen bei psychischer Excitation. Skand Arch Physiol, 48 138, 1926

78 VON MONAKOW, P Blutdrucksteigerung und Niere Dtsch. Arch. klin. Med, 133 129, 1920.

79 WEISS, E Psychosomatic aspects of essential hypertension Acta Psychotherapeutica, 1 13, 1953

80 WEISS, E., ENGLISH, O S., FISCHER, H K., KLEINBART, M., and ZATUCHNI, J The emotional problems of high blood pressure Ann. intern. Med., 37 677, 1952.

81 WEITZ, W and SIEBEN, A Beitrag zur Prognose der essentiellen Hypertension Munch med Wschr, 73: 2197, 1926

82 WOLF, S., and WOLFF, H. G A summary of experimental evidence relating life stress to the pathogenesis of essential hypertension in man. "Hypertension", edited by E T Bell, University of Minnesota Press, Minneapolis, p 288, 1950

83 WOLFF, H. G Life stress and cardiovascular disorders Circulation (N.Y.) 1 187, 1950

CHAPTER VIII

# THE PHYSIOLOGY OF BLOOD PRESSURE REGULATION

The level of the blood pressure depends upon the cardiac output and the resistance of blood vessels; but the factors which control these are numerous and interact complexly.

The cross section of the great veins is much larger than that of the aorta and, ordinarily, the filling pressure of the heart, i.e. the venous pressure in large veins, is a few centimeters of water only. The return of blood to the heart is influenced by the gravitational stresses which occur with changes in posture. Veins and capillaries are under the influence of vasoconstrictor nerves and, in some regions, of vasodilator nerves, but the effects of the vasoconstrictors are more important. The tendency of dependent blood vessels to become dilated when the upright posture is adopted is overcome to an important degree by compensatory sympathetic vasoconstriction. The peripheral resistance is generally considered to be dependent mainly upon the state of contraction or dilatation of arterioles, but there are those who consider that vessels just beyond the arterioles may have a significant effect upon the peripheral resistance. The great vessels near to the heart also have an influence upon the blood pressure level, for they must expand to accommodate the systolic discharge, and recoil to maintain the onward flow of blood in diastole. The aorta and other large vessels which have this reservoir function are described in the German literature as the "Windkessel". It is evident from the free use of this term in the German literature that it would be useful to have available an equivalent expression. It is proposed to refer to this arterial territory as the "arterial reservoir".

## THE OUTPUT FROM THE HEART

### The Cardiac Output in Animal Experiments

In order to separate nervous from non-nervous effects, it is necessary to turn to the Starling heart-lung preparation (Knowlton and Starling, 1912). In the Starling heart-lung preparation the pulmonary circulation remains intact. All the left ventricular outflow is led through an artificial peripheral resistance to a reservoir, and is fed back from the reservoir to the superior vena cava.

In this preparation the heart adjusts its output to the quantity of blood which it receives; it also adjusts the strength of its contraction to the resistance encountered As the Starling heart-lung preparation is not under the influence of the nervous system it becomes evident that there are circumstances in which these adjustments can be made without the assistance of nervous impulses. In the whole animal and in man, although the output is largely determined by the return of blood to the heart by the venous system, sympathetic and parasympathetic nerve impulses influence the rate and output of the heart. As will be seen later, they also influence the return of the blood to the heart.

Knowlton and Starling[93] showed that, within physiological limits, the capacity of the heart to increase its output depended upon the fact that, with any additional inflow of blood, the heart dilated a little, so increasing the initial length of the heart muscle fibres. The output of work is found to be proportional to the presystolic length of the heart muscle fibres; hence, when an increase in the venous filling causes an increase in the diastolic volume of the heart, an automatic adjustment occurs which also increases the strength of the next contraction.

This same mechanism operates when the resistance to outflow is increased If the arterial pressure rises, the heart at first does not expel the whole of the blood supplied to it. The residual blood causes an increase in the presystolic length of the cardiac muscle fibres, thereby increasing automatically the strength of contraction and overcoming the external resistance. The oxygen used by the heart muscle is proportional to the initial length of the cardiac muscle fibre and this, as already stated, is proportional to the work done. In some instances the heart [illegible]
he volume by a r [illegible]
during systole, [illegible]
more complete s[illegible] [illegible]emptying, increases the stroke volume and the cardiac output

It is obvious that such a wonderful proportionality between the load imposed upon the heart and the work done by it can occur only within certain physiological limits. For example, it is possible to increase the venous inflow until the heart is no longer able to pump all the blood supplied to it. Although at first, with increasing venous inflow, the heart dilates and thereby increases its [illegible]
comes [illegible]
by [illegible]
ext[illegible]
[illegible] breakdown occurs when the peripheral resistance rises too high. At first the work done by the heart increases as the resistance is increased, but at a later stage if the peripheral resistance is increased furth[illegible]

Wh[illegible]

heart the filling of the heart offers little resistance to the venous inflow; a few centimeters of water pressure suffice to expand the chambers of the heart during diastole. If, however, the heart is dilated, having an excess of residual blood, the filling pressure may be raised and this resistance to venous filling causes an increase in the general venous pressure.

## Cardiac Output in Man

The stroke volume of the left ventricle in a healthy man at rest is 60 to 100 ml. The minute volume of the heart under basal conditions varies from 3 to 7, and is usually about 5, litres per minute [32]. Cournand et al. (1945) give a cardiac output of 3.12 litres per square meter of body surface per minute. This is called the cardiac index. Although the heart cannot increase its output beyond the blood supplied to it by the venous side, vigorous beating of the heart accelerates the transfer of blood from the arterial to the venous side and a more rapid circulation results.

*The heart rate and the heart output are under nervous control.* An excessive vagal action may slow, or even arrest, the heart beat, so diminishing considerably the cardiac output. Sympathetic acceleration of the heart may or may not be associated with an increase in the cardiac output, depending largely upon whether the return of blood to the heart is increased.

The heart output is raised by infusions of saline and glucose solutions [6, 104, 125, 127] and decreased by venesection [104, 142, 143] and by cuffs on the thighs at about diastolic pressure [104, 143]. In general, increase of heart rate occurring spontaneously or as the result of drug action, causes an increase in the cardiac output and this may take place even when the right auricular pressure is somewhat reduced [104].

*The heart output may be increased 30 to 40 per cent during* digestion and almost 10 times during muscular exercise. Emotion may increase the heart output by about 50 per cent [132]. Normal pregnancy usually increases the minute volume about 50 per cent by the fourth month [25, 131]. Hyperthyroidism may increase the cardiac output by 50 to 100 per cent and an increase is also noted in anaemia [21], and in Paget's disease [46].

It is most important to remember that concurrent physiological adjustments must occur in the peripheral resistance. Were the peripheral resistance to remain unchanged, these increases in cardiac output would inevitably cause proportional increases in the blood pressure: double the output — double the blood pressure.

The volume of residual blood in the ventricles at the end of the systole is often about 130 ml. In the vertical posture the residual blood volume is less than it is in the horizontal posture. There is radiological evidence for this: the heart size is distinctly larger when a person is

lying flat than when the standing posture is adopted. It seems likely [illegible] as in animals, an increase in cardiac output may be [illegible] without increasing [illegible] ense of the residual blood.

## RETURN OF BLOOD TO THE HEART

The distribution of blood between the arteries and the rest of the cardiovascular system depends to an important extent upon the peripheral [illegible] this is high the pressure rises in the arterioles and [illegible] al reservoir ("Wind- [illegible] be an increase in the diastolic volume of the heart.

The extraordinary anatomy of the circulation is, *in itself*, almost a sufficient demonstration of the complexity of circulatory hydrodynamics Schleier (1918) a pupil of Hürthle, for example, pointed out that the cross section of the mesenteric artery is 0.07 sq. cm. in the dog. Branches of the artery had a total cross section which varied from 0.12 to 2 48 sq. cm. The arterioles of the villi had a cross section of 4.18 sq cm. The capillaries had a cross section of 23 8 sq. cm. and the venules 11.69. The branch veins at various points ranged from a total cross section of 5.80 to 0 67 sq. cm. When these veins finally reunited in the mesenteric vein the cross sectional area was 0.28 sq. cm. It is not surprising that the residue of the energy imparted to the blood stream by the left ventricle (*the vis a tergo*) is much diminished by the peripheral resistance.

The return of blood to the heart is strongly influenced by the relationship between the blood volume and the tone of veins, venules and capillaries. The blood volume is important in that if the capacity of systemic veins remains constant and the blood volume increases then the venous pressure must increase and with it [illegible] pressure of the heart. Moreover, the pressure in the great veins is [illegible] Fleisch (1931b) has noted a particular example, namely, that infusion of blood causes dilatation of intestinal veins

Most authorities consider that a considerable increase of the blood volume must take place before the venous pressure rises. It is well known, however, that when large infusions are given in man a rise in venous pressure may occur before there are any other indications of cardiac incapacity. It would be unwise to assume that such rises of

venous pressure always indicate the imminence of a breakdown in cardiac compensation.

Venesection leads to a redistribution of blood and to constriction of blood vessels. Fleisch (1931b) has observed constriction of intestinal veins in animals as a result of venesection. Glaser and McMichael (1940) showed in man that there was an increase in vital capacity following venesection, probably due to a decrease in the volume of reserve blood in the thorax.

Some changes in the venous system are of a simple mechanical character. Venous obstruction causes dilatation of veins, venules and capillaries. These changes may occur without the intervention of the nervous system. When, however, changes in the volume of the venous bed are large enough to be associated with changes in the cardiac output, then regulatory reflexes may be evoked which readjust the state of contraction of all vessels. Nervous reflexes affecting the circulatory system will be considered in more detail later.

The gravitational effects of change in posture influence the intravascular pressure. In man, in the upright posture, the pressure in a vein on the dorsum of the foot is equal to the head of pressure of a column of blood extending down from the manubrium sterni to the vein, provided that the subject is standing immobile (Smirk, 1936). Consequently if pooling of blood in dependent parts is to be restrained, there must be an increase of venous and of capillary tone. Even with the increases of peripheral vascular tone which occur normally in the vertical posture, the human circulation cannot adjust itself completely to the stresses involved in standing immobile or reclining on a tilt-table. When subjects recline on an almost vertical tilt-table the dependent veins and capillaries are dilated and there is additional outward filtration of the protein-free fluid from plasma. This may decrease the plasma volume by an average of 11 per cent according to Thompson, Thompson and Dailey (1928) and by 15 per cent according to Waterfield (1931).

Sjöstrand (1953) states that on changing from the standing posture to the lying posture an average of 643 ml. of blood was shifted from the lower extremities to the rest of the body in five subjects. He emphasizes that 78 per cent of this was taken up in the thorax and distributed between the heart and the lungs. On many occasions, and even with normal subjects, we have noted an increase in the density of pulmonary vessel shadows, as well as in the size of the heart, when subjects transfer from the standing to the lying posture. The volume of blood in the thorax is reported to be reduced by spinal anaesthesia [91] and by positive pressure breathing [11, 53, 59].

The tissue pressure provides an external support for capillaries, veins and venules and may help to prevent pooling of blood in dependent parts. Even slight muscular movements, as distinct from deliberate

exercise, assist the return of blood to the heart, provided the valves in the veins are competent. The magnitude of the effect of muscle tone as distinct from muscle movement on the return of blood to the heart is difficult to decide, as emerges from a critical review by de Vries and Milwidsky (1946).

Some metabolites act directly on peripheral vessels causing local vasodilata-

may take place without the intervention of the nervous system is the contraction of blood vessels exposed to cold There is also the possibility that some tissue metabolites may cause local vasodilatation ...
axon reflex Such
only when a substa
material

If the heart begins to fail, so that with physiological degrees of dilatation it is unable to fulfil the demands made upon it, then the filling pressure of the heart may be increased, so increasing the general

... showed that in cats breathing against a positive pressure, which increases the venous pressure, caused a decrease in blood volume. In man, Henry and co-workers (1948) showed that even in the absence of heart failure, when a person breathes against a positive pressure the general venous pressure is increased, and if this is prolonged, loss of fluid into tissue spaces by filtration causes an appreciable decrease in the blood volume.

Landis and Hortenstine (1950) pointed out in their review on the venous blood pressure that arterioles and veins usually contract or relax in unison with one another. Gollwitzer-Meier (1929) ...
Meier and ...
and
that ... as increased carbon dioxide tension, cause constriction of arterioles and also of veins. Gollwitzer-Meier has shown that in dogs the vasoconstrictor action of $CO_2$ upon a mesenteric vein is of central origin and is abolished by denervation of the vein.

Fleisch (1931a) found that, on reduction of the pressure in the carotid sinus, venous contraction occurs with an increase in the venous return to the heart; and on increasing the pressure in the carotid sinus, the veins dilate and the venous return is decreased.

Rashkind et al (1953) studied the relationship between the peripheral resistance and the venous return. In 100 experiments on 38 dogs they found that in all but one of the ... enous
occu ... This
... f the

central end of [illegible]
line or norad [illegible]
and venomotor activity are correlated. Alexander (1954) made a corresponding study of intestinal vessels. He found that changes in the distensibility of veins are almost always in the same direction as changes in the calibre of arterioles.

*There is good evidence that the volume of blood returned to the heart is determined by a complex regulatory system. In general, increase of blood volume and contraction of veins and venules cause increase in the return of blood to the heart, and thereby increase the cardiac output. Moderate increases of blood volume may occur without increase of cardiac output because of the capacity of the veins and venules to hold an increased volume of blood without increase of venous pressure. It has often been overlooked that the venous side of the circulation plays an important part in securing a cardiac output which conforms to the contemporaneous needs of the body, and that the regulation of the state of contraction or dilatation of veins involves intricate adjustments of nervous and non-nervous mechanisms very similar to those which influence arterioles. Veins, venules and capillaries may expand and contract independently of nervous control, but all of these vessels are under the influence of the autonomic nervous system. The effects of the various influences to which they are exposed are such that usually they are caused to contract and relax in unison with arterioles.*

## RESISTANCE TO THE OUTFLOW OF BLOOD

The resistance to the outflow of blood from the heart involves (1) the resistance to the systolic discharge of blood from the heart, which depends upon the distensibility of the arterial reservoir, and (2) the peripheral resistance, which is the more important.

### The Arterial Reservoir

The blood discharged from the left ventricle in systole must first be accommodated in the aorta and its larger tributaries, and these vessels must stretch to accommodate an additional 60 or 70 ml. of blood, when the heart is beating quietly, but as much as 200 ml when the stroke volume is increased during physical exercise. When, in later life, the large vessels become less distensible, the systolic pressure must rise higher, in order to provide the force necessary to stretch the vessels and induce the requisite increase of volume. Loss of distensibility arises in old people from replacement of muscle and elastic tissue by fibrous tissue. Other arteriosclerotic changes, such as calcification and fibrosis due to atherosclerosis have the same effect. It is generally recognized that decrease of elasticity of the arterial reservoir may lead to a degree of systolic hypertension, but it is not

certain that systolic hypertension is an inevitable consequence of decreased elasticity. The volume of the arterial reservoir increases with age, partly by dilatation and partly by a lengthening of the aorta and other vessels. This increase in the volume of the aorta and of great vessels compensates to some extent for decrease in distensibility in the sense that, with equal elastic properties of the vessel walls, it is easier, by stretching, to accommodate an additional volume of blood in a larger vessel.

Probably decrease in the elasticity of the arterial reservoir does not raise the work of the heart much when a person is at rest but there is no proof that this is true in physical activity, for then large volumes of blood may be discharged into comparatively inelastic vessels and induce peaks of pressure which add to the work of the heart and are, in part, transmitted to peripheral vessels.

It should be pointed out that the distensibility of the arterial reservoir is subject to physiological change. A rise in blood pressure decreases the distensibility of the reservoir and increases the pulse wave velocity as was shown by Bramwell, McDowall and McSwiney (1923), Bramwell, Downing and Hill (1923), and Bramwell (1924). A consequence of this is that in order to secure a given flow of blood there must be a much higher pulse pressure if the diastolic pressure is high than if it is low. The work of the heart is therefore much less at low pressures, in part at least because the energy expended in expanding the arterial reservoir is less than it is at high pressures.

As there is muscle in the aorta and large vessels, the distensibility of the reservoir may be influenced by nervous or humoral stimuli. Such actions may influence the activity of baroceptors in the carotid sinus and aortic arch but otherwise small changes in the calibre of these vessels probably have no important effects on the circulation.

### The Peripheral Resistance

The structure of the blood vascular system is so complex that understanding of the factors which influence its periph[illegible] must be [illegible]

th[illegible] [illegible] by Poiseuille. It states that the pressure varies:

1. directly as the rate of flow
2. directly as the viscosity of the fluid
3. directly as the length of the tube
4. inversely as the fourth power of the radius.

Poiseuille's law cannot be applied quantitatively to a branched, elastic and highly reactive system in which the pressure is pulsatile,

the length and radius of the tubes is unknown and the viscosity is subject to peculiarities related to the presence of cells in the circulating fluid.

Poiseuille's law is, however, most valuable if the limits of its applicability are understood. It enables us to recognize that, other things remaining the same, the resistance of a blood vessel varies inversely as the fourth power of the radius and that very small changes in calibre, scarcely visible microscopically, may change the blood flow appreciably. The predominant role of the blood vessels in regulating the blood pressure is thereby explained.

The formula also indicates that if other things remain the same the pressure varies directly as the flow. If the cardiac output were doubled the blood pressure would be doubled, unless some other adjustments occurred in the circulatory system to prevent this.

A simple formula which has wide application in circulatory dynamics is

$$P = FR$$

where P is the mean pressure F is the rate of flow and R is the resistance.

If a pressure $P_1$ is opposed by a pressure $P_2$ at the outlet of a tube, then $P_1 - P_2 = FR$
or alternatively

$$F = \frac{P_1 - P_2}{R}$$

## THE NON-NERVOUS INFLUENCES AFFECTING THE PERIPHERAL RESISTANCE

The state of contraction or dilatation of arterioles is the major force determining the peripheral resistance. Investigations, involving acute experiments only, suggest that the peripheral resistance is largely dependent upon the flow of sympathetic impulses to blood vessels. In fact it may be said that, in the healthy intact animal, the non-nervous factors which preserve a peripheral resistance serve only as a background, foundation or support for the neurogenic mechanism which determines the magnitude of the peripheral resistance and thereby the level of the blood pressure.

Not only is there eventually a recovery of vascular tone in vessels following sympathectomy but the sensitivity of the vessels to the vasoconstrictor action of adrenaline is greatly increased, as was shown by Elliott (1905) and Freeman et al. (1934). It is not certain whether pre- and post-ganglionic denervation have similar effects. White et al. (1936) thought post-ganglionic denervation was the more effective but Fatherree et al. (1940) considered pre- and post-ganglionic denervation were equally effective. Duff (1952) obtained evidence that, in man,

the blood vessels of skeletal muscle were also hypersensitive to adrenaline after pre- and post-ganglionic denervation.

Dale and Richards (1918) showed that in cats the blood vessels, after complete degeneration of their nerve supply, became unusually sensitive to the vasodilator action of histamine and acetylcholine as well as to the vasoconstrictor action of adrenaline.

## Recovery of Tone in Denervated Blood Vessels

[illegible]

the superior cervical ganglion the turgescence of the blood vessels [illegible] ished within several days and might be inconspicuous on the day after operation In the course of time sympathectomized vessels recover their tone. Very extensive, almost complete, sympathectomies in dogs by Bacq, Brouha and Heymans (1929) [illegible] crease of the blood p[illegible] to activity, and the [illegible] al. (1929) reported somewhat similar experiments on cats.

Armin and co-workers (1953) have provided a likely explanation for these happenings. When a vessel possesses its normal sympathetic nerve supply, it appears that a certain amount of acetylcholine is synthesized and released peripherally, and the release is independent of central nervous stimulation. This keeps the artery dilated except when sympathetic vasoconstrictor stimulation, by the release of sympathomimetic substance, overcomes the dilating effect of the acetylcholine. When the sympathetic influence is removed by sympathetic nerve section, the release of acetylcholine gradually passes off and because of this the vessel recovers tone, even though no sympathetic impulses flow to it. This hypothesis may account in part for the fact that, after sympathectomy for hypertension, the large falls of blood pressure observed soon after the operation are rarely maintained It is interesting, however, that once drug toleration has developed, the hypotensive action of ganglion blocking agents seems to be maintained indefinitely.

## Distensibility of Blood Vessels

[illegible] studying the reac- [illegible] stasis obscures [illegible] depend on ner[illegible] [illegible] can be described which concern the non-neurogenic activity of blood vessels.

The flow of blood through perfused vessels can be studied in pre-

the length and radius of the tubes is unknown and the viscosity is subject to peculiarities related to the presence of cells in the circulating fluid.

Poiseuille's law is, however, most valuable if the limits of its applicability are understood. It enables us to recognize that, other things remaining the same, the resistance of a blood vessel varies inversely as the fourth power of the radius and that very small changes in calibre, scarcely visible microscopically, may change the blood flow appreciably. The predominant role of the blood vessels in regulating the blood pressure is thereby explained.

The formula also indicates that if other things remain the same the pressure varies directly as the flow. If the cardiac output were doubled the blood pressure would be doubled, unless some other adjustments occurred in the circulatory system to prevent this.

A simple formula which has wide application in circulatory dynamics is

$$P = FR$$

where P is the mean pressure F is the rate of flow and R is the resistance.

If a pressure $P_1$ is opposed by a pressure $P_2$ at the outlet of a tube, then $P_1 - P_2 = FR$
or alternatively

$$F = \frac{P_1 - P_2}{R}$$

## THE NON-NERVOUS INFLUENCES AFFECTING THE PERIPHERAL RESISTANCE

The state of contraction or dilatation of arterioles is the major force determining the peripheral resistance. Investigations, involving acute experiments only, suggest that the peripheral resistance is largely dependent upon the flow of sympathetic impulses to blood vessels. In fact it may be said that, in the healthy intact animal, the non-nervous factors which preserve a peripheral resistance serve only as a background, foundation or support for the neurogenic mechanism which determines the magnitude of the peripheral resistance and thereby the level of the blood pressure.

Not only is there eventually a recovery of vascular tone in vessels following sympathectomy but the sensitivity of the vessels to the vasoconstrictor action of adrenaline is greatly increased, as was shown by Elliott (1905) and Freeman et al. (1934). It is not certain whether pre- and post-ganglionic denervation have similar effects. White et al (1936) thought post-ganglionic denervation was the more effective but Fatheree et al. (1940) considered pre- and post-ganglionic denervation were equally effective. Duff (1952) obtained evidence that, in man,

the blood vessels of skeletal muscle were also hypersensitive to adrenaline after pre- and post-ganglionic denervation.

Dale and Richards (1918) showed that in cats the blood vessels, after complete degeneration of their nerve supply, became unusually sensitive to the vasodilator action of histamine and acetylcholine as well as to the vasoconstrictor action of adrenaline.

## Recovery of Tone in Denervated Blood Vessels

Chronic experiments reveal the importance of processes which do not depend upon the activity of the nervous system and which, in certain circumstances, assume control of blood vessels. Claude Bernard in 1852 recognized that after division of the cervical sympathetic chain below the superior cervical ganglion the turgescence of the blood vessels diminished within several days and might be inconspicuous on the day after operation. In the course of time sympathectomized vessels recover their tone. Very extensive, almost complete, sympathectomies in dogs by

al (1929) reported somewhat similar experiments on cats

Armin and co-workers (1953) have provided a likely explanation for these happenings When a vessel possesses its normal sympathetic nerve supply, it appears that a certain amount of acetylcholine is synthesized and released peripherally, and the release is independent of central nervous stimulation. This keeps the artery dilated except when sympathetic vasoconstrictor stimulation, by the release of sympathomimetic substance, overcomes the dilating effect of the acetylcholine. When the sympathetic influence is removed by sympathetic nerve section, the release of acetylcholine gradually passes off and because of this the vessel recovers tone, even though no sympathetic impulses flow to it. This hypothesis may account in part for the fact that, after sympathectomy for hypertension, the large falls of blood pressure observed soon after the operation are rarely maintained It is interesting, however, that once drug toleration has developed, the hypotensive action of ganglion blocking agents seems to be maintained indefinitely.

## Distensibility of Blood Vessels

In the whole animal or man there is difficulty in studying the reactions of blood vessels which are not dependent on nervous action because, as already indicated, the efficient inter- [illegible]

sta[illegible]

dep[illegible]

cor[illegible]

[illegible] of blood vessels.

[illegible] of blood through perfused vessels can be studied in pre-

parations in which the vessels are no longer under the action of the nervous system. It is important to know whether arterioles are stretched by the intravascular pressure because, if they are stretched, a rise in intravascular pressure will tend (in the absence of homeostasis) to cause a decrease in the peripheral resistance.

There has been appreciable dispute about this. Whittaker and Winton (1933) and Pappenheimer and Maes (1942) thought that the resistance to flow through blood vessels was unaltered by variations

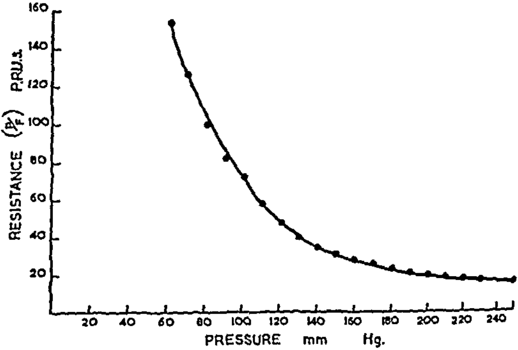



Fig. VIII 1

*The resistance of the blood vessels of the rat hindquarter preparation* perfused with neosynephrine hydrochloride 1/100,000, plotted against the perfusion pressure. The resistance decreases with increasing intravascular pressure. (Doyle, A E., Circulation Research, 1 375—370, 1953, by permission).

in pressure. More recently Nichol et al. (1951) found that the resistance was almost independent of the pressure so long as this was well above the critical closing pressure *. Levy et al. (1954), working on

* The term "critical closing pressure" is used to denote the lowest pressure at which a circulation through a vascular bed can be maintained *It is found when* [illegible] when the perfusion pressure is reduc- [illegible] e critical closing [illegible] fusion pressure, [illegible] oter, but further information may be obtained by consulting the references cited and also in publications by Burton (1951) and Christophers (1954)

Probably the critical closing pressure, *which varies with the state of contrac-* [illegible] in the opening up and in the closing off [illegible] *tions in meta-*

dogs, found that when the moderator reflexes were eliminated, there was a linear relationship between pressure and flow in the systemic vascular bed, and the total peripheral resistance remained relatively constant, despite pressure changes. Green et al. (1944) however,

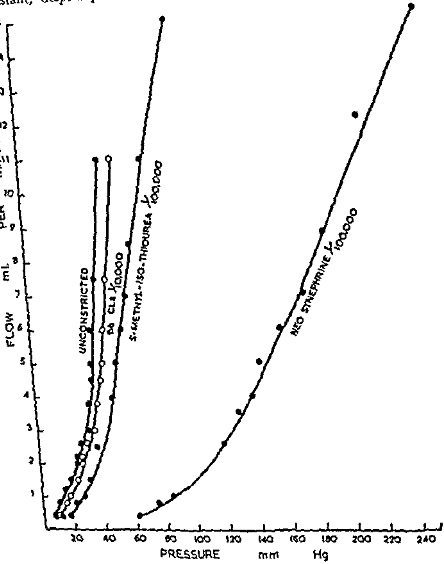



Fig VIII 2

Flow-pressure [illegible]
perfused wit [illegible]
added (Doy [illegible] by permission).

considered that a decrease in resistance occurred in response to increasing intravascular pressure. Similar results were obtained earlier,

in the frog, by Schleier (1922). Most of the observations have been made by methods in which the venous outflow is recorded. This, however, is subject to the error that the accumulation of oedema fluid may interfere with the results.

Doyle (1953) studied the effect of perfusing the isolated rat's hindquarters through the aorta with a Krebs-Hensleit solution containing 6 per cent Dextran (average molecular weight 75,000) at constant flow, using a rotary pump. When the rates of perfusion were slow and pressures were not much above a critical closing pressure there was a rapid change in resistance with increasing intravascular pressure Fig. VIII 1. With higher pressures, induced by adding vasoconstrictors to the perfusion fluid, although the rate of change in resistance as the pressure rose was less, there was still a decrease in vascular resistance with increasing intravascular pressure Fig. VIII 1. It seems likely that the use of the constant flow method may have explained some of the differences between Doyle's results and those of other workers. A constant flow perfusion method probably gives a closer approximation to conditions in the whole animal, where if some vessels close down a rise of pressure will occur because of increase in resistance. The relation between flow and perfusion pressure is shown in Fig. VIII 2. In this series of experiments the vessels were constricted, by adding pressor agents to the perfusate. The rate of decrease of resistance with increase of intravascular pressure diminished but, nevertheless, a decrease in the resistance was still observed.

If Doyle's experiments on rat blood vessels may be applied to human blood vessels, one may anticipate that, in the absence of regulatory reflexes, the gravitational increment in the intravascular pressure in the legs, brought about by assumption of the erect posture, will expand arterioles as well as other vessels and thereby decrease the peripheral resistance in the legs. In the intact human, sympathetic regulatory reflexes cause contraction of arteriolar muscle so that the peripheral resistance is not much altered. It seems probable that in man a rise of blood pressure brought about by an increase in cardiac output will tend to induce a simple mechanical dilatation of arterioles which does not depend upon the action of the nervous system. Such a dilatation would decrease the peripheral resistance and would assist the nervous regulators in antagonizing blood pressure increases.

Attention has been redirected to an important observation by Bayliss (1902) who showed that a sudden rise of the arterial pressure caused the volume of the hind limb of dogs, cats and rabbits to decrease below the original level, following a preliminary increase. This effect persisted after denervation and was thought by Bayliss to be due to a response of the muscular walls of the blood vessels. Greenfield and Patterson (1954) made observations on blood flows in the human forearm following exposure to negative pressures. They

found changes in blood flow which suggested contraction in response to the stretching of vascular muscle but they did not regard their results as conclusive.

### Other Non-nervous Influences Affecting the State of Contraction of Peripheral Blood Vessels

McDowall (1935) has shown that carbon dioxide acts locally as a vasodilator, although centrally it stimulates the medulla and causes vasoconstriction. Histamine acts peripherally as a vasodilator in man though in rabbits some peripheral arteries are constricted when histamine is applied locally.

### Comment

*The great vessels close to the heart require to be distensible as they have to accommodate temporarily the blood expelled during cardiac systole. Where the elasticity of this arterial reservoir is diminished there will be an increase in pulse pressure and the work of the heart will be increased. The resistance to the outflow of blood, however, depends mainly on the peripheral resistance. Normally the control of the peripheral resistance depends mainly on regulatory mechanisms which operate through the autonomic nervous system (These are described in more detail later.) The blood vessels are also influenced by non-nervous means.*

*Although there is some conflict of evidence, it seems likely that the extent to which a blood vessel will contract under a given stimulus is restricted by the intravascular pressure, which tends to stretch the vessel and diminish peripheral resistance. As vasoconstriction elevates the blood pressure, a balance is struck between the degree of blood vessel constriction and the intravascular pressure, in the sense that, if the intravascular pressure had not risen, the vasoconstriction would have involved greater narrowing of the blood vessels.*

Vasoactive substances may have an important effect on the state of contraction of blood vessels. Additional information on vasoactive substances is contained in Chapters IX and XI.

## NERVOUS REGULATION OF THE CIRCULATION IN ANIMALS

Nervous control over the activity of the heart [illegible]
complex [illegible]
also [illegible]

in the frog, by Schleier (1922). Most of the observations have been made by methods in which the venous outflow is recorded. This, however, is subject to the error that the accumulation of oedema fluid may interfere with the results.

Doyle (1953) studied the effect of perfusing the isolated rat's hindquarters through the aorta with a Krebs-Hensleit solution containing 6 per cent Dextran (average molecular weight 75,000) at *constant flow, using a rotary pump. When the rates of perfusion were* slow and pressures were not much above a critical closing pressure there was a rapid change in resistance with increasing intravascular pressure Fig. VIII 1. With higher pressures, induced by adding vasoconstrictors to the perfusion fluid, although the rate of change in resistance as the pressure rose was less, there was still a decrease in vascular resistance with increasing intravascular pressure Fig. VIII 1. It seems likely that the use of the constant flow method may have explained some of the differences between Doyle's results and those of other workers. A constant flow perfusion method probably gives a closer approximation to conditions in the whole animal, where if some vessels close down a rise of pressure will occur because of increase in resistance. The relation between flow and perfusion pressure is shown in Fig. VIII 2. In this series of experiments the vessels were constricted, *by adding pressor agents to the perfusate. The rate of decrease of* resistance with increase of intravascular pressure diminished but, nevertheless, a decrease in the resistance was still observed.

*If Doyle's experiments on rat blood vessels may be applied to* human blood vessels, one may anticipate that, in the absence of regulatory reflexes, the gravitational increment in the intravascular pressure in the legs, brought about by assumption of the erect posture, will expand arterioles as well as other vessels and thereby decrease the peripheral resistance in the legs. In the intact human, sympathetic regulatory reflexes cause contraction of arteriolar muscle so that the peripheral resistance is not much altered. It seems probable that in man a rise of blood pressure brought about by an increase in cardiac output will tend to induce a simple mechanical dilatation of arterioles which does not depend upon the action of the nervous system. Such a dilatation would decrease the peripheral resistance and would assist the nervous regulators in antagonizing blood pressure increases.

Attention has been redirected to an important observation by Bayliss (1902) who showed that a sudden rise of the arterial pressure caused the volume of the hind limb of dogs, cats and rabbits to decrease below the original level, following a preliminary increase. This effect persisted after denervation and was thought by Bayliss to be due to a response of the muscular walls of the blood vessels. Greenfield and Patterson (1954) made observations on blood flows in the human forearm following exposure to negative pressures. They

y cause vasoconstriction or dilatation and changes in heart rate. Autonomic functions have been attributed also to the orbito frontal cortex (areas 9 to 14) and the anterior cingulate gyrus (area 24) which latter is on the mesial surface of the frontal lobe.

The *hypothalamus* lies between the cerebral peduncles. It is above and in close proximity to the pituitary gland and, as the name implies, it lies inferior to the optic thalamus. The anterior part of the hypothalamus lies superior to the decussation of the optic chiasma, posteriorly it includes the mammillary bodies; and between the chiasma and the mammillary bodies lies the tuber cinereum.

Stimulation of the hypothalamus has shown that this region contains cell stations of the sympathetic and parasympathetic systems (Ranson and Magoun, 1939). Stimuli applied to the posterior and lateral hypothalamic nuclei were reported as causing sympathetic acceleration of the heart and rise of blood pressure; and stimulation [illegible] the tuber [illegible] there is a band extending from the supraoptic area back to the mammillary bodies which, when stimulated electrically, causes sympathetic vasodilatation in the skeletal muscle of cats. These authors do not favour the idea of anatomically separate regions in the hypothalamus as centres of sympathetic and parasympathetic activity.

Gellhorn et al. (1956) have reported some interesting experiments on the hypothalamus in cats. They find evidence that central [illegible] [illegible] rise of blood pressure and increase of heart rate. Lesions of the posterior (sympathetic) part cause fall of blood pressure and pulse slowing. The two regions appear to act reciprocally, stimulation of one leading to inhibition of the other.

Lesions of the anterior part of the [illegible] pulse slowing which follo[illegible] sions of the posterior part [illegible] acceler[illegible] The [illegible] in a[illegible] [illegible] be expected to occur with [illegible] lesions of the hypothalamus in man. The experiments are, however, of great interest and should promote further work on the subject.

In the *medulla* there are also cell stations of the sympathetic

R

circulatory system. Thus any change in the action of the heart, or in the level of the blood pressure, usually has an effect upon most other parts of the circulatory system. The rate and strength of contraction of the heart may be modified by either [illegible] sympathetic [illegible] medulla, either as the result of [illegible] activity or in other ways. Arterioles, veins and minute vessels may be affected by sympathetic vasoconstrictors Fig. VIII 3. Vasodilators may be parasympathetic or sympathetic.

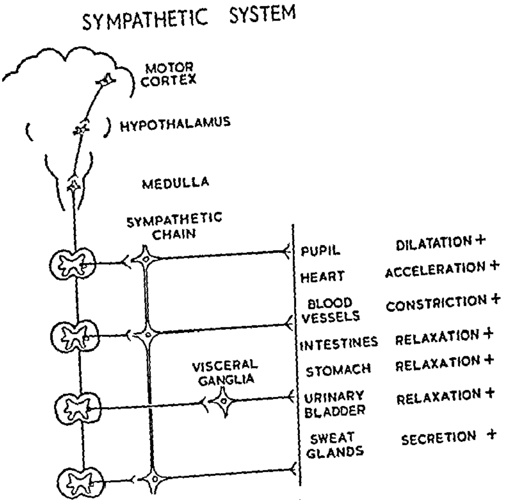



Fig VIII 3

Connections of the sympathetic nervous system Effects of sympathetic stimulation shown on the right of the diagram.

## Nervous Connections

Although the precise connections are unknown, there is ample evidence that the cerebral cortex makes connections with both the sympathetic and the parasympathetic supply to the heart, with the

from T9 and 10 or 10 and 11; and the lowest splanchnic nerve from T12.

The *post-ganglionic neurones* originating in ganglia go directly, without further relay, to the organ which they innervate.

## Chemical Mediators

In 1904 T. R. Elliott referred to the resemblance between the effects of administering adrenaline and stimulating sympathetic nerves He advanced the fruitful suggestion that sympathetic nerves might exercise their effects by releasing *chemical substances* at their endings. This discovery opened a new chapter in physiology, for the basic idea of chemical mediation has contributed to our knowledge of synaptic transmission as well as to the understanding of nerve action at the periphery.

There seems to be good evidence that sympathetic stimulation leads to the liberation of noradrenaline at some sympathetic nerve endings. Proximity of the noradrenaline so released to its site of action is probably the explanation of most of the differences between the effects [illegible] ; noradrenaline or causing [illegible] It may be that in some [illegible] sympathetic nerve endings, [illegible]

endings. The wisdom of the body may have [illegible] a wide choice of chemical mediators, appropriate to the tasks which need to be performed. A striking example is the *occurrence of cholinergic* transmission at the endings of the sympathetic supply to sweat glands. Further remarks on adrenaline and noradrenaline are in the section relating to phaeochromocytomas.

It would appear that *acetylcholine* is the chemical transmitter at parasympathetic nerve endings. Acetylcholine is also, apparently, the transmitter at the endings of all preganglionic autonomic nerves, and it is therefore liberated in all autonomic ganglia and in the suprarenal medulla.

Uvnas (1954) recently reviewed present knowledge concerning sympathetic vasodilators. He says that the neurones take their origin in the motor cortex and pass to the [illegible]

[illegible] neurones. All the postganglionic neurones of the vasodilator system are, he thinks, cholinergic. Burn (1932) also obtained evidence that the endings of some sympathetic vasodilator nerves are likely to be cholinergic, for he observed that vasodilatation of the dog's hind limb occurred on stimulation of the lumbar sympathetic chain, and this effect was increased by eserine and prevented by atropine.

The question of whether there are adrenergic vasodilators has not

nervous system. Ranson and Billingsley (1916) found points on the floor of the fourth ventricle which, when the appropriate region was stimulated electrically, would cause rises or falls of the blood pressure. There is good evidence of a vasoconstrictor centre in the medulla but the vasodilator effects which result from electrical stimulation may be due to stimulation of the afferent pathways of a vasodilator reflex, rather than to direct stimulation of a centre. Ranson and Billingsley (1916) showed that, in cats, the pathway of vasodilator fibres from the medulla down to cells in the lateral column was in the anterolateral columns.

In the *spinal cord* there are sympathetic reflex centres which may cause large blood pressure rises, even when they are completely cut off from centres in the medulla, hypothalamus or cerebral cortex. The cell stations of the sympathetic preganglionic fibres are all located in *the grey matter of the lateral horns* at levels between T1 and L4. If a cat is kept alive after section of the cervical cord, the blood pressure rises again to an approximately normal level; but if the spinal cord is then destroyed, the blood pressure falls to a very low level.

Hermann, Morin and Vial (1936, 1937) found that, with ascending destruction of the spinal cord, the blood pressure was usually well maintained until 7D was reached. If destruction was carried higher than this the blood pressure fell. When the entire thoracic and lumbar cord was destroyed in chronic experiments the vascular tone returned soon after the operation, and a relatively normal blood pressure was maintained for over a year. It is evident that the subsidiary centres in the spinal cord are capable of assuming vasomotor control. These lower centres are stimulated by $CO_2$ and are inhibited if $CO_2$ is removed by overventilation. Malméjac et al. (1948) also showed that the lower centres were stimulated by hypoxia.

*There is good evidence that levels of integration of the sympathetic system are to be found in the cerebral cortex, hypothalamus, medulla and spinal cord. There is also good evidence that higher centres exert some, at least, of their effects through the intermediation of lower centres. The extent to which a higher centre can by-pass a lower centre is not yet clear.* Beattie et al. (1930), however, showed in the cat, that there were uninterrupted neurones connecting the hypothalamus to the lateral column of grey matter in the spinal cord

The *preganglionic fibres* leave the spinal cord in the white (medullated) rami and pass to ganglia of the sympathetic chain or by the splanchnic nerves (which are preganglionic) to the abdominal ganglia (coeliac, mesenteric, renal, suprarenal etc.). Preganglionic neurones on their way to the abdominal ganglia may pass through ganglia of the sympathetic chain, but do not relay until they reach their destination. In man there are three *splanchnic nerves* on each side of the body: the greater splanchnic nerve from T5 to T9 or 10; the lesser splanchnic nerve

## NERVOUS REGULATION OF THE CIRCULATION IN MAN

Unfortunately, lack of information makes it inadvisable to confine the remarks made in this section to direct observations made in man, but as far as is possible it will be made clear which observations have been made in man and which, although made in experimental animals, seem likely to be applicable.

It has been pointed out already that some of the activities of the heart and blood vessels are regulated by their sympathetic and parasympathetic innervations and these have connections in the spinal cord, medulla, hypothalamus and cerebral cortex. On the afferent side the nervous regulation of the circulation involves baroceptors sensitive to pressure changes and chemoreceptors. The location and action of receptors varies from one animal to another and difficulties of investigation have precluded a full study in man.

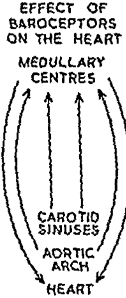



Fig VIII 4

Connections of the baroceptors Afferent stimuli from the carotid sinuses and aortic arch cause slowing of the heart by a vagal pathway.

### Receptor Zones: Baroceptors and Chemoreceptors

(1) *The carotid sinus* —In man the carotid sinus region is innervated by the intercarotid branch of the glossopharyngeal, by the vagus, by sympathetic fibres from the inferior cervical ganglion (de Castro 1928 Tchibukmacher, 1938) and occasionally from the hypoglossal (Danielopolu and Manescu, 1928). Anastomoses are often present

yet been settled. Dale (1913) showed that, after ergotoxin, stimulation of the splanchnic nerves causes dilatation of the vessels of the intestines and a fall of blood pressure, even after removal of the suprarenal glands. The administration of adrenaline, after paralyzing sympathetic vasoconstrictors with ergotoxin (Dale, 1906) or dibenamine (Nickerson and Goodman, 1947) also causes vasodilatation. The above observations at first suggested that there were adrenergic vasodilators.

Since Dale made his observations with ergotoxin and adrenaline, evidence has [illegible] constrictor (Folkow and Uvnäs, 1948; Goodman and Gilman, 1955) and its constrictor action annulled but not reversed by ergotamine nor by dibenamine (Folkow and Uvnäs, 1948. Goodman and Gilman, 1955). There is, however, some uncertainty about the facts. Lands et al. (1950) noted that vasodepressor responses could be obtained in dogs after administering appropriate doses of noradrenaline and the depressor action was enhanced by F 933. Stehle and Ellsworth (1937) found that in decapitate cats the pressor action of noradrenaline was sometimes slightly reversed by ergotoxin, and West (1949) also observed reversal by ergotoxin in cats. Wells and Rall (1948) noted reversal of the action of noradrenaline by N-(2-bromoethyl)-N-ethyl-1-naphthalene-methylamine (SY [illegible]

*Although the matter cannot be regarded as settled, it seems very likely that some sympathetic vasodilator neurones have cholinergic endings. It is possible that some vasodilator neurones have adrenergic endings, but more work on the subject is needed. Investigation in animals and the application to man are alike made more difficult by important species differences in the distribution and significance of sympathetic vasodilator nerves (Burn, 1938). Our knowledge of sympathetic vasodilator effects in man must depend largely on clinical studies.*

It is of interest that Villasante et al (1954) report evidence suggesting that the rises of blood pressure induced by stimulation of the central end of the vagus [illegible] which [illegible] is [illegible] on [illegible] Further evidence from the same group of workers has been published by Jiménez Díaz et al (1954)

Bayliss (1900, 1901) showed in dogs that excitation of the peripheral end of a cut posterior root in the lumbar region caused vasodilatation in the hind limb on the same side. Lewis and Marvin (1927) obtained evidence that such antidromic impulses passing along sensory nerves cause vasodilatation in the region of the nerve terminals by releasing a vasodilator substance.

*Aortic body.* — It has been shown in animals that there is an aortic body somewhat similar in structure to the carotid body.

... and it seems that the ... dioxide ... an also ... able to ... ease in ... d after ... es from this body run in the vagus nerve.

The existence of an aortic body in man lacks demonstration.

*Coronary chemoreflex.* — (Von Bezold and Hirt, 1867). The Von Bezold reflex appears to be excited chiefly by pharmacological means, notably by the administration of veratrum alkaloids, and there is not much direct evidence that it occurs naturally. Nevertheless, the dramatic physiological effects which occur on administering minute quantities of pure veratrum alkaloids, either in man or in lower animals, suggest the possibility that an important reflex, the exact function of which is yet undetermined, has been revealed by drug action (see Chapter XVI for further detail). The injection of veratrum alkaloid in minute amounts (½—1 μg. of veratridine) into a coronary artery has given rise to bradycardia and profound hypotension. There is, of course, a risk in drawing the conclusion that a naturally occurring reflex has been stimulated ...

suggested, that the cardiac receptors activated by veratrum alkaloids may normally respond to stretch of the ventricular walls. It is also possible that they are chemoreceptors.

The afferent pathway of the coronary reflex is in the vagus nerves. The vagus is responsible for some of the efferent effects, for example, the bradycardia. Other actions, such as increased blood flow through limb vessels, depend on sympathetic inhibition.

*Pulmonary chemoreflex.* — Cramer (1915) believed that the Von Bezold effect was brought about by stimulation of nerve endings in the lungs. Subsequent work has confirmed that veratrum alkaloids and some other chemical substances, when introduced into the pulmonary circulation, cause reflex bradycardia and hypotension. These effects, however, are less formidable than those which follow excitation of the coronary reflex. Intravenous injection of veratrum alkaloids in man may cause bradypnoea. It is possible that this reflex operates in the human — certainly veratrum alkaloids have very similar actions in man and lower animals.

between the nerves. The general impression has been that the inhibitory reflexes are conveyed largely through the glosso-pharyngeal nerves. Fig. VIII 4.

(2) *Aortic receptors* have been described in man. According to Heymans et al. (1933), the nerve from the aortic arch may be either isolated, or the fibres may ascend in the vagus, or in the cervical sympathetic. Cardiac receptors have been described in man by Danielopolu but as yet the finding is unconfirmed.

(3) *The Bainbridge reflex* has not been demonstrated in man. In animals distension of the right auricle leads to stimulation of afferent vagus fibres and causes heart acceleration Bainbridge considered that by this reflex the activity of the heart was governed by the rate of filling from systemic veins

(4) *Mesenteric, coeliac, hepatic receptors and receptors in limb vessels.* — As yet the above receptors have not been demonstrated in man but, were means of investigation available, it seems likely that the presence of additional baroceptive zones would be revealed in the human. In animals, however, there is evi- [illegible]

[illegible]

described baroceptors in the territory of the coeliac and mesenteric arteries in dogs. Rein (1943) has described sensitive zones in the hepatic artery

## Chemoreflexes

True chemoreflexes are those which are brought into action by conditions which may occur spontaneously in health or disease. They may be stimulated vicariously by drug action or other means.

*Carotid body.* — The carotid body occurs in man and in most animals used for experiments. In man it lies behind the bifurcation of the common carotid artery. It consists of a mass of chromaffin cells and of numerous nerve fibres derived from the superior cervical ganglion and from the glosso-pharyngeal nerve. In animals the chemoreceptors in the carotid body are influenced by changes of the tensions in blood of oxygen and of carbon dioxide (Heymans et al 1931; Bernthal 1932; Heymans et al. 1933). Both anoxaemia and carbon dioxide excess cause a rise in the blood pressure. Palme (1944) considers that adrenaline or a similar substance may be liberated from the carotid body and, acting on the nearby carotid sinus, may influence its reactions to pressor stimuli. Kezdi (1954a) in experiments on dogs found that electrical stimulation of isolated sympathetic fibres, or of a superior cervical ganglion connected only to the carotid sinuses, led to a decrease of systemic pressure. In addition to the release of noradrenaline at sympathetic nerve endings he thinks the chromaffin cells of the carotid body may perhaps liberate adrenaline and affect barosensitive areas of the arterial wall. His main point is that the superior cervical ganglion may play a part in circulatory homeostasis. Further information about the carotid body is available in the review by Heymans (1955).

*Aortic body.* — It has been shown in animals that there is an aortic body somewhat similar in structure to the carotid body.

... and it seems that the
... carbon dioxide
... c body can also
... oe was able to
... ive increase in
... occurred after
... rent fibres from

The existence of an aortic body in man lacks demonstration.

*Coronary chemoreflex.* — (Von Bezold and Hirt, 1867). The Von Bezold reflex appears to be excited chiefly by pharmacological means, notably by the administration of veratrum alkaloids, and there is not much direct evidence that it occurs naturally. Nevertheless, the dramatic physiological effects which occur on administering minute quantities of pure veratrum alkaloids, either in man or in lower animals, suggest the possibility that an *important* reflex, the exact function of which is yet undetermined, has been revealed by drug action (see Chapter XVI for further detail). The injection of veratrum alkaloid in minute amounts (¼—1 *μg* of veratridine) into a ...
artery has given rise to ...
is, of course, a risk in dra...
reflex has been stimulated, for veratridine stimulates stretch receptors in the lungs and by making them fire continuously, leads to arrest of respiration. This latter is not a natural reflex. It is possible, as Jarisch suggested, that the cardiac receptors activated by veratrum alkaloids may normally respond to stretch of the ventricular walls. It is also possible that they are chemoreceptors.

The afferent pathway of the coronary reflex is in the vagus nerves ...
... example,
... through

*Pulmonary chemoreflex.* — Cramer (1916) believed that the Von Bezold effect was brought about by stimulation of nerve endings in the lungs. Subsequent work has confirmed that veratrum alkaloids and some other chemical substances, when introduced into the pulmonary circulation, cause reflex bradycardia and hypotension. These effects, however, are less formidable than those which follow excitation of the coronary reflex. Intravenous injection of veratrum alkaloids in man may cause bradypnoea. It is possible that this reflex operates in the human — certainly veratrum alkaloids have very similar actions in man and lower animals.

**Carotid Sinus Reflexes**

In 1799 Caleb Hillier Parry, a physician of Bath, made the clinical observation that pressure on the carotid artery caused *slowing of the heart beat*. It is generally agreed that the carotid sinuses assist regulation of the blood pressure level and probably they are concerned particularly with protection of the brain from excessive rises and falls of blood pressure. Control over the blood pressure level during change in posture is brought about, in part, through the activity of the carotid sinus and aortic baroceptors. That the function of the carotid sinus is regulatory, restraining excessive rises and falls was first clarified by the work of Hering (1923, 1930).

Franke (1951) working in Wollheim's laboratory finds that carotid sinus pressure, in hypersensitive human subjects, leads to a decrease in stroke volume, prolongation of systole and enlargement of the heart. The venous pressure is increased due to the cardiac inhibition.

The fall in blood pressure on carotid sinus pressure has two components, decrease in the cardiac output and peripheral vasodilatation. The decrease in cardiac output is brought about by vagal action and, to a large extent, can be prevented by atropinization. Vagal effects on the heart are also lacking when carotid sinus pressure is exercised in patients with complete heart block [129]. But in patients who are heavily atropinized, or have complete heart block, a fall in the blood pressure occurs on carotid sinus stimulation [129] and it is thought that this blood pressure fall is due to decrease in the sympathetic nervous tone of blood vessels.

When during an operation on an innominate aneurysm or for some other reason, a human common carotid artery is obstructed below the level of the carotid sinus, the blood pressure may rise considerably, though with unilateral obstruction there is an early return to normotension. In one of my patients the original blood pressure level was restored in two or three days. The blood pressure rises also with obstruction by digital pressure applied to the carotid arteries below the level of the carotid sinuses.

Koch (1931), Heymans, Bouckaert and Regniers (1933) and Hauss, Kreuzinger and Asteroth (1949) showed in animals that the effect of the arterial blood pressure on the carotid sinus receptors was exercised by the stretching of the sinuses. If, however, there is a rise of pressure on both sides of the carotid sinus arterial wall, so that no stretching occurs then the receptors are not stimulated. There seems no reason to believe that it would be otherwise in man. It appears from animal experiments that the carotid sinus acts mainly if not exclusively as a restraining influence on the circulation. The pressor effects which occur when the endosinusal pressure falls are due to temporary suspension of the normal inhibitory action of the carotid sinuses. Kezdi (1954b) considers that, normally, the vasomotor centre is set

to regulate the blood pressure at a higher level than the normal blood pressure, and that the normal activities of the centre are being restrained by the discharge of inhibitory impulses from the baroceptors. It is not surprising, therefore, that in animals and in man large blood pressure rises may occur when local anaesthetics are injected around the carotid sinus region in order to block the carotid sinus nerves. Lampen (1949) and Kezdi (1953), for example, observed large rises of blood pressure

pressure were obtained, but within a few days these were already subsiding, and in seven to twelve days the blood pressure reached pre-operative levels. It is of interest that, in these operated patients, digital pressure below the carotid sinuses still elevated the blood pressure. This raised the question of whether, in man, section of the well-defined carotid sinus nerve does in fact denervate the sinus completely.

Meurer (1949) reported that the application of adrenaline to the carotid sinus in man led to a fall in the arterial blood pressure. In animal experiments it has been shown on many occasions that the application of drugs such as adrenaline, noradrenaline and pitressin, which contract blood vessels, tend to cause a marked fall in the systemic arterial pressure and to reduce or suppress the pressor reflexes which normally follow a decrease in the pressure within the carotid sinus (Heymans et al. 1933; Palme 1936). It was found also that adrenolytic drugs reversed or suppressed the action of adrenaline and noradrenaline applied locally to the carotid sinus (Heymans 1954). Drugs which relax the smooth muscles, such as papaverine, when applied to the carotid sinus induced a rise of blood pressure (Heymans and Van den Heuvel-Heymans 1950). While experiments of this kind have not all been carried out in man it seems likely that the observations are applicable to the human situation.

Adrenaline causes contraction of the arterial walls of the carotid sinus and is thought thereby to stimulate the pressor receptors and cause a fall of blood pressure. Here a difficulty arises, the facts are not easily explained by supposing that the receptors are responsive to the degree of stretch of the sinus wall. The sinus wall should be contracted by adrenaline so acquiring a smaller calibre which, in the absence of adrenaline, would correspond with a lower blood pressure. Yet, paradoxically, the response to local application of adrenaline is a fall of blood pressure. It has been suggested that receptors are intimately bound up with the smooth muscle so that its contraction

causes a stimulation of the receptors. It seems unlikely that the many pressor and depressor substances selected for their effects on the smooth muscle of blood vessels should all, when applied locally, have a direct action on the receptors. It is more likely that they act indirectly by contracting or relaxing muscle in the sinus wall.

An observation in cats by Ead, Green and Neil (1952) is probably applicable to the human situation. The authors studied the effect of pulsatile and non-pulsatile blood flow in the carotid sinus at the same mean pressure. When the aortic nerves were intact there was no demonstrable change in the systemic pressure on changing from a pulsatile to a steady flow. When, however, the aortic nerves were cut, change from a pulsatile to a non-pulsatile state caused a reflex rise in the systemic pressure. The authors also concluded that, even at mean pressures less than 70 or 80 mm. Hg the carotid sinus is still sending out inhibitory impulses.

In this connection it is interesting to consider the hypothesis that hardening of the carotid artery by decreasing pulsation in the vessel may give rise to increases of the blood pressure. It should be recollected, however, that arterial hardening is unlikely to be confined to the carotid sinus region. Hardening of the arterial reservoir ("Windkessel") as a whole will increase the pulse pressure. Therefore, whenever the carotid sinus is less distensible, it is likely that the distending force will be greater also. It may be difficult, therefore, to predict the final effect on the blood pressure regulation of the hardening of large arteries, including the carotid artery and its baroceptive zone.

It is of interest that, in some patients, Weiss and Baker (1933) found that stimulation of the carotid sinus may give rise to cerebral symptoms such as faintness, giddiness and unconsciousness, even when the blood pressure fall is inconspicuous. Such symptoms may be pronounced in cases with hypertensitivity of the carotid sinus. Presumably this is due to cerebral vasoconstriction.

Additional references to the literature are to be found in Heyman's (1955) monograph.

### Blood Pressure Raising Reflex from Muscle.
(Alam and Smirk, 1937)

This reflex depends upon the accumulation of exercise metabolites in voluntary muscle. The reflex is elicited by exercise of arm or leg muscles during arrest of the circulation to the exercising muscles by an inflated sphygmomanometer cuff (Fig. VIII 5). The reflex persists after cessation of exercise, provided that the limb circulation remains [illegible] metabolites in muscles. [illegible] y and [illegible]. The the circulation arrested at the moment of cessation [illegible]

authors expressed the view that the rise of blood pressure in many subjects preceded the onset of pain.

Harpuder and Stein (1943) also remarked that a fairly marked rise in both systolic and diastolic levels is observed long before the pain threshold is reached. With a sufficient amount of exercise of ischaemic muscle pain certainly occurs,

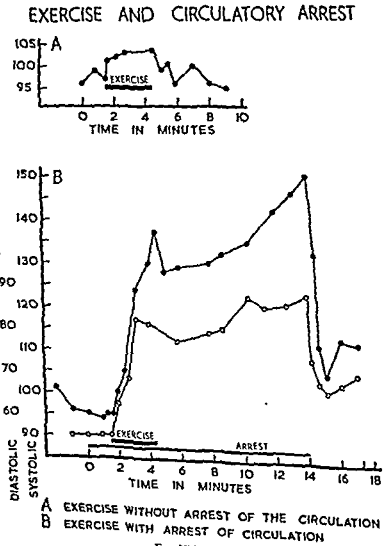



Fig. VIII 5

Reflex rise of blood pressure induced by exercise of ischaemic muscles *Arrest* refers to a period of circulatory arrest in an arm brought abo[illegible] sphygmomanometer cuff.

E[illegible]
180
unc [illegible]
193 [illegible]

and with further exercise, pain and blood pressure rise are associated together. Some writers have considered that the reflex is a variety of pain reflex. Alam and Smirk (1938a), however, showed that, when pains are induced by electrical stimulation and in certain other ways, and are greater in intensity than the pain from exercised ischaemic muscle, the blood pressure rise from the exercise during ischaemia is the greater.

Observations by Korner (1952) suggest that the blood pressure raising reflex from muscle performs a physiological function in improving the blood flow to muscles during exercise. Dr. V. Cable and I [66] also obtained evidence of this. Ordinarily if an arm is raised to a vertical position, exercise of its forearm muscles soon induces claudication pain. If, however, we first perform exercise with arrested circulation of the left arm, the amount of pain in the elevated right arm is decreased. This is due to the reflex elevation of the blood pressure.

It was shown (Alam and Smirk, 1938a) that, as an average, the responses to similar amounts of exercise with arrested circulation are greater in essential hypertension than in health, and greater in old than in young subjects (fig. VIII 6).

Fleisch and Weger (1940) were able to demonstrate this reflex in anaesthetized dogs using faradization to exercise the muscles. They cite unpublished observations by Weger who showed that the reflex also could be elicited in anaesthetized patients by faradization of the muscles.

A pulse accelerating reflex from muscle (Alam and Smirk, 1937) arises when muscle metabolites accumulate during exercise made with the circulation of a limb arrested. This reflex depends to an important extent upon having a considerable bulk of muscle involved in the exercise. Interest attaches to the question of whether these are genuine reflexes or merely a form of non-specific sensory stimulation which causes blood pressure increase. The author is inclined to think that the reflexes serve a physiological purpose, that they may be elicted in the absence of pain but that when pain is present the reflex effects are roughly proportional to the pain induced. It seems likely that many regions of the body are capable of discharging impulses which influence the nervous regulation of the circulation.

**Blood Pressure Raising Reflexes from Cold.** (Hines and Brown, 1932)

Mosso in 1895 referred to some observations made in his laboratory by Dr. Colombo who noted that a cold bath (5°C) increased the blood pressure (presumably systolic) by about 30 mm. Hg.

Hines and Brown (1932) devised a cold pressor test based upon the fact that immersion of a hand in ice-cold water causes a rise of blood pressure. The extent to which pain is responsible for the blood pressure rise has been much debated.

Their technique was designed to standardize the stimulus and is described as follows (Hines and Brown, 1936):

"The subject is allowed to rest in a supine position in a quiet room for 20 to 60 minutes. Several readings of the blood pressure are taken until a basal level has been approximated. The cuff of the sphygmomanometer is placed on one

arm of the subject, and the opposite hand is placed in ice water (4 degrees Centigrade) to a point just above the wrist. Readings of the blood pressure are taken at the end of 30 seconds and again at the end of 60 seconds. The maximal reading obtained while the hand is in the ice water is taken as the index of the response".

[illegible]

obtained painlessly.

Dr. Irvine, at my suggestion, has studied the effect upon the blood pressure of cold stimuli which did not cause pain. The cold was applied to one or both legs below mid thigh le[illegible]
tion was arrested [illegible]
others small blood [illegible]
is immersed in tep[illegible]

[illegible]

Consistent results [illegible]

[illegible]

Hines has now had experience with this test for more than 20 years and has followed for 10 to 20 years the subsequent progress of individuals who have been tested. He has made adjustments in his criteria for distinguishing between *normal* and abnormal reactions. In a recent publication Hines (1951) lays his main emphasis on changes in diastolic pressure. He defines hyporeactors as those who, with the cold pressor test, exhibit diastolic pressure rises of 10 mm. Hg or less, normoreactors show rises of 10 to 20 mm. Hg, *hyperreactors* show rises of more than *20 mm. Hg.*

Among individuals with "*normal*" blood pressure (diastolic always less than 100 mm. Hg *except* in the cold pressor test) he found that the occurrence of hypertension after 15 years was 54 per cent among hyperreactors, 17 *per cent* among normoreactors and *none* among hyporeactors. In *general* Hines (1951) concludes that hyporeactors seldom develop permanent hyper*tension* and hyperreactors *often do.*

Hines (1951) also considers established hypertensives as being mostly hyperreactors. He reports the mean diastolic blood pressure rise in 841 patients with essential hypertension as 30.0 mm. Hg and

in 1015 with normal or usually normal blood pressures as 13.2 mm. Hg. It would be interesting to know if the ages of the patients in some of these groups were comparable.

Recently Windesheim, Roth and Hines (1955) have used intra-arterial pressure recordings to confirm earlier work and mention that the cold pressor test is reduced by ganglion blocking agents but not by protoveratrine, reserpine or hydralazine.

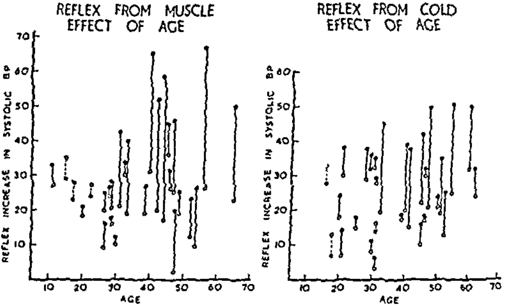



Fig VIII 6

*Left.* The effect of the reflex from muscle upon the blood pressure at different ages Dots are systolic pressure, circles are diastolic pressure increases

*Right.* The effect of the local application of cold upon the blood pressure at different ages. Dots are systolic pressure, circles are diastolic pressure increases. (Redrawn from Alam, M., and Smirk, F. H., Clin Sci., 3 259, 1938b)

Without doubt the average degree of reactivity to the cold pressor test is greater in elderly than in young people (Pickering and Kissin, 1936; Alam and Smirk, 1938b; Feldt and Wenstrand, 1942; Russek, 1943; Russek and Zohman, 1945) (Fig. VIII 6). There has been some difference of opinion as to whether, when subjects of comparable ages are studied, the cold pressor responses in essential hypertension are larger than in normotensives. Pickering and Kissin (1936) and Todd (1944) found no difference. Thacker (1940) and Alam and Smirk, (1938b) found that the reactions were greater in the patients with essential hypertension.

The latter authors pointed out that although the mean rise of blood pressure in patients with essential hypertension exceeded the mean rise in normotensives of the same age group, there were many hyper-reactive normotensives and several patients with essential hypertension who had only small rises of blood pressure. Alam and Smirk

(1938b) and Miller and Bruger (1939) found the response to the cold pressor test was smaller in renal than in essential hypertension.

This much is clear — it does not seem reasonable to regard a person as a probable candidate for hypertension because he shows an excessive reaction to the cold pressor test, but there seems to be some reason

is referred to in chapter III.

## Blood Pressure Raising Reflexes from Viscera

Most of the evidence relating to reflex nervous elevations of the blood pressure are concerned ultimately with reactions which take place in the vasomotor centres, probably for the greater part in the medulla. There is, however, clear evidence, in man as well as in lower animals, that reflexes below this level may induce large blood pressure rises. Guttmann and Whitteridge (1947) referred to the very high blood pressures which may be induced reflexly from distension of the bladder in patients who have complete lesions of the spinal cord, at or above T5, with an intact cord below this level. The blood pressure rise is associated with vasoconstriction in the toes, with marked vasodilatation in the neck, face and nasal mucosa. Thompson and Witham (1948) found that the blood pressures in spinal cord injuries were more labile when the lesions were above the level of the fifth dorsal segment. They observed that, not only urinary retention, but also bowel distension could provoke blood pressure elevation. Corresponding observations were made by Ciliberti, Goldfein and Rovenstine (1954). Further detailed observations come from Cunningham, Guttmann, Whitteridge and Wyndham (1953). They made a detailed study of three paraplegic patients with lesions below T6 and found that the blood flow in muscles, which were supplied by sympathetic fibres coming from the isolated cord, showed a considerable decrease when the bladder was distended. In contrast, muscles supplied by fibres coming from above the lesion, which were therefore controlled by the vasomotor centre, showed

patients, with lesions at T1 and C7, respectively, who showed an increase in the forearm blood flow but a great decrease in the flow through the skin of the fingers.

Evidence that sympathetic constriction of the vessels of the skin may be induced by bladder distension in healthy subjects has been published by Adams-Ray and Norlén (1951). More, cited Cunningham et al. (1953) states that when the bladder pressure rises above 50 mm Hg there is a widespread vasoconstriction of the skin, but large volumes of fluid may be present in the bladder without causing

cutaneous constriction provided the bladder pressure remains low.

### Vasoconstrictor Reflex Following Deep Inspiration

Goetz (1935) and Bolton et al. (1936) described the occurrence of vasoconstriction in all four limbs following a deep breath. The vasoconstriction does not occur in a sympathectomized limb. The reflex, according to Bolton et al. (1936), did not occur in the lower limbs of a paraplegic. Gilliatt, Guttmann and Whitteridge (1948), however, in a study of paraplegic patients found that the inspiratory vasoconstriction reflex is a spinal phenomenon which can be demonstrated in patients with a complete break in the functional continuity of the spinal cord above the level of the sympathetic outflow to the hands.

### Sympathetic Vasodilator Reflexes in Man

In 1890 Sewall and Sanford showed that heating one arm led to vasodilatation in the fingers of the opposite arm, but Pickering (1933) showed that this vasodilatation depended upon the return of warmed blood to the general circulation.

Lewis and Pickering (1933) found that in patients with Raynaud's phenomenon involving the hands, they were able to obtain evidence of the presence of vasodilator nerves. When the arms of such patients were cool, and an ulnar nerve anaesthetized, it was found that general body warming caused dilatation of the skin vessels of the hands, except over the distribution of the anaesthetized ulnar nerve. Evidently such results cannot be explained by removal of vasoconstrictor tone. Fatherce and Allen (1938) using methods somewhat similar to those of Lewis and Pickering also obtained evidence of the presence of sympathetic vasodilators in man, in the legs as well as the arms. The papers by Wilkins and Eichna (1941) and by Barcroft and Edholm (1945) indicate the presence of peripheral vasodilators. Evidence of a vasodilator supply to the muscle of the human forearm was produced by Barcroft and Edholm (1945) who noted that, during fainting, there was a fall in blood pressure and increased blood flow through the human forearm. This vasodilatation did not take place if the arm had lost its sympathetic innervation (Fig. IV 1). Hence they thought the vasodilatation was due to the presence of sympathetic vasodilator fibres to the muscles. It seems, therefore, that in man there is evidence indicating the presence of sympathetic vasodilator fibres to skin and to muscle.

### Further Remarks on Circulatory Homeostasis in Man

The widespread use of ganglion blocking agents in the treatment of hypertension made it necessary to discuss their effects on circulatory homeostasis in the chapters devoted to therapeutics. The availability of ganglion blocking agents suitable for use in man has provided a wonderful opportunity of examining the extent to which

the human circulation is dependent on homeostatic reflexes; and the information so obtained (see Chapter XVIII) should be considered also as being the conclusion of the present chapter, as well as being part of the chapter on clinical pharmacology.

## References


1 ADAMS-RAY, J., and NORLEN, G Bladder distension reflex with vasoconstriction in cutaneous venous capillaries Acta physiol. scand, 23: 95,

2 ALA[illegible]

3 ALAM, M., and SMIRK, F H [illegible] pulse accelerating, reflex from voluntary muscle due to a lesion of the spinal cord. Clin Sci, 3: 247, 1938a.

4 ALAM, M, and SMIRK, F. H Blood pressure raising reflexes in health, essential hypertension, and renal hypertension Clin. Sci., 3: 259, 1938b

5 ALEXANDER, R S The participation of the venomotor system in pressor reflexes. Circulation Research, 2: 405, 1954.

6 ALTSCHULE, M D, and GILLIGAN, D R The effects on the cardiovascular system of fluids administered intravenously. J. clin. Invest., 16: 859, 1937

7 ANREP, G V Lane Medical Lectures: Studies in Cardiovascular Regulation Stanford University Press, California, 1936.

8 ARMIN, J, GRANT, R T, THOMPSON, R H. S, and TICKNER, A. An explanation for the heightened vascular reactivity of the denervated rabbit's ear J Physiol (Lond), 121 603, 1953.

9 AYMAN, D, and GOLDSHINE, A D Cold as a standard stimulus of blood pressure A study of normal and hypertensive subjects. New Engl. J. Med, 219. 650, 1938.

10 BACQ, Z. M, BROUHA, L, and HEYMANS, C. Réflexes vaso-moteurs d'origine sino-cardotidienne chez le chat sympathectomisé C. R. Soc. Biol (Paris), 111 152, 1932

11 BAHNSON, H T Air Force Tech Report 6528, 518, 1951. Cited by Sjöstrand T, Physiol Rev, 33 202, 1953

12 BARCROFT, H, and EDHOLM, O G On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting J. Physiol. (Lond.), 104: 161, 1945

12a BAYLISS, W M. On the origin from the spinal cord of [illegible]

12b BAY[illegible]

13 BAY[illegible] On the local reactions of the arterial wall to changes of internal pressure J Physiol. (Lond), 28: 220, 1902

14 BEATTIE J., BROW, G. R, and LONG, C N. H Physiological and anatomical evidence for the existence of nerve tracts connecting the hypothalamus with spinal sympathetic centres Proc. roy. Soc. B, 106: 253, 1930.

15 BERNARD, C De l'influence du système nerveux grand sympathique sur la chaleur animale C R Acad Sci (Paris), 34: 472, 1852.

16 BERNTHAL, T. G. Changes in volume flow of blood resulting from chemical stimulation of the carotid sinus. Amer. J. Physiol., 101: 6, 1932.
17 BOLTON, B., CARMICHAEL, A, and STÜRUP, G. Vaso-constriction following deep inspiration. J. Physiol. (Lond), 86: 83, 1936.
18 BRAMWELL, J. C. Arterial elasticity in man. Quart. J. Med., 17: 225, 1924.
19 BRAMWELL, J. C., DOWNING, A. C., and HILL, A. V. The effect of blood pressure on the extensibility of the human artery. Heart, 10: 289, 1923.
20 BRAMWELL, J. C., McDOWALL, R. J. S, and McSWINEY, B. A. The variation of arterial elasticity with blood pressure in man. Proc. roy. Soc. B., 94: 450, 1923.
21 BRANNON, E. S, MERRILL, A. J., WARREN, J. V., and STEAD, E. A, Jr The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J. clin Invest., 24: 332, 1945.
22 BURN, J. H. On vaso-dilator fibres in the sympathetic, and on the effect of circulating adrenaline in augmenting the vascular response to sympathetic stimulation J. Physiol. (Lond.), 75: 144, 1932
23 BURN, J. H. Sympathetic vasodilator fibres. Physiol Rev., 18: 137, 1938.
24 BURTON, A. C On the physical equilibrium of small blood vessels Amer. J Physiol., 164: 319, 1951.
25 BURWELL, C S, STRAYHORN, W. D, FLICKINGER, D, CORLETTE, M. B, BOWERMAN, E P, and KENNEDY, J A Circulation during pregnancy Arch intern. Med., 62. 979, 1938
26 CABLE, J. V., and SMIRK, F. H. Unpublished observations.
27 CABLE, J V., and SMIRK, F. H. Blood-pressure-raising reflexes in hysterical anaesthesia. Brit. med J, 2. 874, 1941.
28 CANNON, W. B., NEWTON, H F, BRIGHT, E M., MENKIN, V., and MOORE, R M. Some aspects of the physiology of animals surviving complete exclusion of sympathetic nerve impulses Amer. J Physiol., 89: 84, 1929.
29 CHESLEY, L. C, and CHESLEY, E R Cold pressor test in pregnancy Surg. Gynec Obstet., 69: 436, 1939.
30 CHRISTOPHERS, A J An analysis of the phenomenon known as "critical closing pressure". Med. J Aust., 2. 460, 1954
31 CILIBERTI, B J, GOLDFEIN, J., and ROVENSTINE, E. A Hypertension during anesthesia in patients with spinal cord injuries Anesthesiology, 15. 273, 1954.
32 COURNAND, A, RILEY, R. L, BREED, E S, BALDWIN, E DE F., and RICHARDS, D. W., Jr. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. J. clin. Invest., 24· 106, 1945
33 CRAMER, W On the action of veratrum viride — with some remarks on the interrelationship of the medullary centres J. Pharmacol, 7: 63, 1915.
34 CUNNINGHAM, D J. C, GUTTMANN, L, WHITTERIDGE, D, and WYNDHAM, C H. Cardiovascular responses to bladder distension in paraplegic patients J Physiol. (Lond), 121 581, 1953
35 DALE, H H On some physiological actions of ergot J Physiol (Lond.), 34. 163, 1906
36 DALE, H. H On the action of ergotoxine, with special reference to the existence of sympathetic vasodilators J Physiol. (Lond), 46. 291, 1913
37 DALE, H. H, and RICHARDS, A N. The vasodilator action of histamine and of some other substances. J. Physiol (Lond), 52 110, 1918
38 DANIELOPOLU, D Cited by HEYMANS, C, BOUCKAERT, J. J., and REGNIERS

... la zone homologue cardio-aortique: Phy-
..., 1933.
... n der Carotid;
39 ... r sinus caroticus
... exp Med, 63.
143, 1928.
40 DAWES, G. S., and COMROE, J. H., Jr. Chemoreflexes from the heart and lungs. Physiol. Rev., 34: 167, 1954.
41 DE ...
42 DE ... review. Acta med. orient. (Tel-Aviv), 5: 56, 1946.
43 DOYLE, A. E. The estimation of peripheral vascular resistance to varying rates of flow in the isolated rat hindquarter. Circulation Research, 1: 375, 1953
44 DUFF, R S Supersensitivity of the blood vessels of human skeletal muscle to adrenaline following sympathectomy. J. Lab. clin. Med., 40: 794, 1952.
45 EAD, H W, GREEN, J H., and NEIL, E. A comparison of the effects of pulsatile and non-pulsatile blood flow through the carotid sinus on the reflexogenic activity of the sinus baroceptors in the cat J. Physiol. (Lond.), 118: 509, 1952
46 EDHOLM, O. G, HOWARTH, S, and MCMICHAEL, J Heart failure and bone blood flow in osteitis deformans. Clin Sci, 5: 249, 1945.
47 ELIASSON, S, FOLKOW, B, LINDGREN, P., and UVNÄS, B. Activation of sympathetic vasodilator nerves to the skeletal muscles in the cat by ... 77: ...3, 1951.
48 ... J. Physiol.
49 ... 12 401, 1905.
50 FATHEREE, T J, ADSON, A W, and ALLEN, E V. The vasoconstrictor action of epinephrine on the digital arterioles of man before and after sympathectomy Surgery, 7: 75, 1940.
51 FATHEREE, T J, and ALLEN, E. V Sympathetic vasodilator fibers in the upper and lower extremities — Observations concerning the mechanism of indirect vasodilatation induced by heat Arch intern. Med, 62 1015, 1938
52 F... 194..
53 FENN, W O, OTIS, A B, RAHN, H., CHADWICK, L. E, and HEGNAUER, A H Displacement of blood from the lungs by pressure breathing Amer J Physiol., 151: 258, 1947
54 FLEISCH, A Venomotorenzentrum und Venenreflexe I. Mitteilung Pflügers Arch ges Physiol., 225, 26, 1930.
55 FLEISCH A Venomotorenzentrum und Venenreflexe. II. Mitteilung. Blutdruckzügler und Venenreflexe Pflügers Arch. ges. Physiol., 226: 393, 1931a
56 FLEISCH, A Venomotorenzentrum und Venenreflexe III. Mitteilung. Pflügers Arch. ges Physiol, 228: 399, 1931b
57 FLEISCH, A, and WEGER, P. Des nerfs afférents dans la paroi des vaisseaux sanguins. Rev. med Suisse rom, 40 489, 1940

58 FOLKOW, B., and UVNÄS, B. The chemical transmission of vasoconstrictor impulses to the hind limbs and the splanchnic region of the cat Acta physiol. scand., 15: 365, 1948.
59 FOWLER, R. C., GUILLET, M., and RAHN, H. Air Force Tech Report 6528, 622, 1951. Cited by Sjöstrand, T., Physiol. Rev., 33: 202, 1953
60 FRANKE, H. Zur Herzdynamik der hypersensitiven herzhemmenden Carotissinus-syndroms. Z. klin. Med., 148: 211, 1951.
61 FREEMAN, N. E., SMITHWICK, R. H., and WHITE, J. C. Adrenal secretion in man — The reactions of the blood vessels of the human extremity, sensitized by sympathectomy, to adrenalin and to adrenal secretion resulting from insulin hypoglycemia. Amer. J. Physiol, 107: 529, 1934.
61a GELLHORN, E., NAKAO, H., and REDGATE, E. S. The influence of lesions in the anterior and posterior hypothalamus on tonic and phasic autonomic reactions. J. Physiol (Lond.). 131: 402, 1956.
61b GILLIATT, R. W., GUTTMAN, L., and WHITTERIDGE, D. Inspiratory vasoconstriction in patients after spinal injuries. J Physiol. (Lond.), 107: 67, 1948.
62 GLASER, E M, and McMICHAEL, J. Effect of venesection on the capacity of the lungs Lancet, 2: 230, 1940
63 GOETZ, R. H. Der Fingerplethysmograph als Mittel zur Untersuchung der Regulationmechanismen in peripheren Gefassgebieten. Pflügers Arch ges Physiol, 225: 271, 1935.
64 GOLDRING, W, and CHASIS, H. Hypertension and hypertensive disease The Commonwealth Fund, New York, 1944
65 GOLL ... ung in ihrer ... 04, 1929
66 ... ctorische ... ur den Kreislauf Klin
67 GOODMAN, L. S., and GILMAN, A. The pharmacological basis of therapeutics. The Macmillan Company, New York, 1955
68 GREEN, H. D, LEWIS, R. N, NICKERSON, N. D, and HELLER, A L Blood flow, peripheral resistance and vascular tonus, with observations on the relationship between blood flow and cutaneous temperature. Amer J Physiol, 141: 518, 1944
69 GREENFIELD, A D M, and PATTERSON, G C Reactions of the blood vessels of the human forearm to increases in transmural pressure. J Physiol (Lond), 125: 508, 1954
70 GUTTMANN, L, and WHITTERIDGE, D Effects of bladder distension on autonomic mechanisms after spinal cord injuries Brain, 70: 361, 1947.
71 HARPUDER, K, and STEIN, I D Studies on the nature of pain arising from an ischemic limb. I. Clinico-experimental observations II Biochemical studies Amer Heart J, 25: 429, 1943
72 HAUSS, W H., KREUZINGER, H, and ASTEROTH, H Über die Reizung der Pressorezeptoren im Sinus Caroticus beim Hund Z. KreislForsch., 38: 28, 1949
73 HENRY, J P, HENDRICKSON, I, MOVITT, E, and MEEHAN, J P Estimations of the decrease in effective blood volume when pressure breathing at sea level. J clin. Invest, 27: 700, 1948
74 ... herzhemmenden ... h Ges inn Med,
75 ... mit Rucksicht auf ... : 7, 1930.

76 HER[illegible]

77 HERMANN, H., MORIN, G., and VIAL, J. Les régulations périphériques chez le chien sans moelle II. Évolution de la pression artérielle après la destruction de la moelle dorso-lombo-sacrée. Arch. int. Physiol., 44: 125, 1937.

78 HEYMANS, C. Some new aspects of reflex blood [illegible]

79 [illegible] 7 119, 1955

80 HEYMANS, C., and BOUCKAERT, J. J. Presso-sensibilité réflexogène des zones vasculaires thoraco-abdominales. Ann. Physiol., 14: 356, 1938.

81 HEYMANS, C., BOUCKAERT, J. J., FARBER, S., and HSU, F. Y. Spinal vasomotor reflexes associated with variations in blood pressure. Amer. J. Physiol., 117: 619, 1936

82 HEYMANS, C. [illegible]

83 HEY[illegible]

84 HEY[illegible] [BOUC]KAERT, J. J., and WIERZUCHOWSKI, M. Réflexes vasomoteurs médullaires d'origine vasculaire barosensible. [illegible]

85 [illegible]

86 HINES, E. A., Jr. Vascular reactivity and hypertensive disease. Hypertension, edited by E. T. Bell, University of Minnesota Press, Minneapolis, 1951

87 HINES, E. A., Jr., and BROWN, G. E. A standard stimulus for measuring vasomotor reactions. Its application in the study of hypertension. Proc. Mayo Clin., 7: 332, 1932

88 HINES, E. A., Jr., and BROWN, G. E. The cold pressor test for measuring the reactibility of the blood pressure: data concerning 571 normal and hypertensive subjects. Amer. Heart J., 11: 1, 1936

89 HYMAN, C., and GOODMAN, J. Fluid shifts in animals during pressure breathing. Amer. J. Physiol. 155 [illegible]

90 [illegible]

91 [illegible] The effect of some anaesthetic agents on the circulation in man — With special reference to the significance of pulmonary blood volume for the circulatory regulation. Acta chir. scand., 101: 501, 1951.

92 KEZDI, P. Sinaortic regulatory system — Role of pathogenesis of essential and malignant hypertension. Arch. [illegible]

93 KEZDI, P. [illegible] trac[illegible] Circ[illegible]

94 KEZDI, [P.] Neurogenic hypertension in man — Transient hypertension and

tachycardia caused by disruption of the carotid sinus: Review of buffer nerve mechanism. Arch. intern. Med., 94: 122, 1954b.

95 KNOWLTON, F. P., and STARLING, E. H. The influence of variations in temperature and blood-pressure on the performance of the isolated mammalian heart. J. Physiol. (Lond.), 44: 206, 1912.

96 KOCH, E. Die reflektorische Selbststeuerung des Kreislaufes. Theodor Steinkopf, Dresden, 1931. Cited by Heymans, C., A Ciba Foundation Symposium on Hypertension, J. & A. Churchill Ltd., London, 1954

97 KORNER, P. I. Reflex regulation of post-exercise blood pressure. Aust J exp Biol. med. Sci., 30: 385, 1952

98 LAMPEN, H. Experimentelle Sinusblockade bei den verschiedenen Hochdruckformen. Verh. dtsch. Ges. KreislForsch., 15: 88, 1949

99 LANDIS, E. M., and HORTENSTINE, J. C. Functional significance of venous blood pressure. Physiol Rev, 30: 1, 1950

100 LANDS, A M., LUDUENA, F. P., ANANENKO, E., and GRANT, J I A comparison of the sympathetic inhibitory action of 1-(3, 4-dihydroxyphenyl)-2-aminoethanol with that of several of its analogs Arch int Pharmacodyn, 83: 602, 1950

101 LEVY, M N., BRIND, S H., BRANDLIN, F. R, and PHILLIPS, F. R. The relationship between pressure and flow in the systemic circulation of the dog Circulation Research, 2. 372, 1954.

101a LEWIS, T., and MARVIN, H. M. Observations relating to vasodilatation arising from antidromic impulses, to herpes zoster and trophic effects Heart, 14: 27, 1927.

102 LEWIS, T, and PICKERING, G W Vasodilation in the limbs in response to warming the body, with evidence for sympathetic vasodilator nerves in man Heart, 16: 33, 1933.

103 McDOWALL, R J S The nervous control of the blood vessels. Physiol Rev, 15: 98, 1935

104 McMICHAEL, J., and SHARPEY-SCHAFER, E P. Cardiac output in man by a direct Fick method — Effects of posture, venous pressure change, atropine, and adrenaline. Brit. Heart J, 6. 33, 1944

105 MALMÉJAC, J, CHARDON, G, and GROSS, A Excitation des centres vasomoteurs médullaires par le déficit en oxygène C R Soc Biol (Paris), 142. 1102, 1948

106 MEUREN, H. Kreislaufuntersuchungen beim Menschen nach Resektion des Karotis-sinus-nerven Verh dtsch Ges KreislForsch, 15: 77, 1949

107 MILLER, J. H, and BRUGER, M The cold-pressor reaction in normal subjects and in patients with primary (essential) and secondary (renal), hypertension Amer Heart J, 18: 329, 1939

108 MORE. Unpublished observations Cited by Cunningham, D J C, Guttmann, L, Whitteridge, D, and Wyndham, C. H., J. Physiol (Lond), 121: 581, 1953

109 MOSSO, A. Sphygmomanomètre pour mesurer la pression du sang chez l'homme. Arch. ital. Biol, 23: 177, 1895

110 NICKERSON, M, and GOODMAN, L S Pharmacological properties of a new adrenergic blocking agent: N,N-dibenzyl-β-chloroethylamine (dibenamine) J. Pharmacol., 89. 167, 1947

111 NICHOL, J, GIRLING, F., JERRARD, W, CLAXTON, E B, and BURTON, A C. Fundamental instability of the small blood vessels and critical closing pressures in vascular beds Amer. J Physiol, 164. 330, 1951

112 PALME, F. Des Adrenalins auf den Sinus-caroticus. Z. Kreisl Forsch, 28 173, 1936

113 PALME, F. Zur Funktion der branchiogenen Reflexzonen fur Chemo- und Pressoreception. Z. ges. exp. Med., 113: 415, 1944

114 PAPPENHEIMER, J. R., and MAES, J. P. A quantitative measure of the vasomotor tone in the hindlimb muscles of the dog. Amer. J. Physiol 137. 187, 1942.

115 PICKERING, G W. The vasomotor regulation of heat loss from the human skin in relation to external temperature. Heart, 16: 115, 1933

116 PICKERING, G. W., and KISSIN, M Effects of adrenalin and of cold in human hypertension Clin Sci, 2 201, 1936

117 RAN[illegible]

118 RANSON, S. W., and MAGOUN, H. W. The hypothalamus. Ergebn. Physiol, 41: 56, 1939

119 RASHKIND, W J, LEWIS, D. H, HENDERSON, J B., HEIMAN, D. F., and DIETRICK, R. B. Venous return as affected by cardiac output and total peripheral resistance Amer. J. Physiol, 175: 415, 1953

120 REIN, H Vasomotorische Schutzreflexe aus dem Stromgebiet der Arteria Hepatica. Pflügers Arch ges. Physiol, 246: 866, 1943.

121 RUSSEK, H. I The significance of vascular hyperreaction as measured by the cold-pressor test. Amer. Heart J., 26: 398, 1943.

122 RUSSEK, H I, and ZOHMAN, B L Influence of age upon blood pressure response to the cold-pressor test Amer. Heart J., 29: 113, 1945

123 SCHLEIER, J. Der Energieverbrauch in der Blutbahn Pflügers Arch ges Physiol, 173. 172, 1918.

124 SCHLEIER, J. Der Einfluss gefasserregender Mittel auf die Elastizität der Arterienwand Pflügers Arch. ges Physiol, 193: 610, 1922.

125 SEGERS, M, and WALSH, J. P. Modification of the cardiac output after intravenous injection of hypertonic glucose solution. Amer. J. med. Sci, 217· 494, 1949

126 SEWALL, H, and SANFORD, E Plethysmographic studies of the human vasomotor mechanism when excited by electrical stimulation J Physiol (Lond), 11· 179, 1890

127 [illegible] J. Circulatory overloading [illegible] Brit. med. J., 2: 304, 1942

128 S[illegible] blood and their significance [illegible] Rev., 33: 202, 1953

129 S[illegible] unpublished observations

130 SMIRK, F H Observations on the causes of oedema in congestive heart failure Clin Sci, 2 317, 1936

131 STANDER, H J, and CADDEN, J F The cardiac output in pregnant women. Amer J Obstet Gynec, 24· 13, 1932.

132 STEAD, E A, Jr., WARREN, J V, MERRILL, A. J., and BRANNON, E S. The cardiac output in male subjects as measured by the technique of right atrial catheterization — Normal values with observations on the effect of anxiety and tilting J clin. Invest, 24. 326, 1945.

133 STEHLE, R L, and ELLSWORTH, H C Dihydroxyphenyl ethanolamine (arternol) as a possible sympathetic hormone J. Pharmacol, 59. 114 1937

134 TCHIBUKMACHER, N B Surgical anatomy of carotid sinus nerve and intercarotid ganglion Surg Gynec Obstet 67· 740, [illegible]

135 THACKER, E A [illegible] sures among [illegible] Heart J, 2 [illegible]

136 THOMPSON, C E, and WITHAM, A C Paroxysmal hypertension in spinal cord injuries New Engl J Med, 239: 291, 1948

137 THOMPSON, W O, THOMPSON, P K, and DAILEY, M. E. The effect of

posture upon the compostition and volume of the blood in man. J clin. Invest., 5: 573, 1928.

138 TODD, R. L. The cold pressor test. J.-Lancet, 64: 410, 1944.

139 UVNÄS, B. Sympathetic vasodilator outflow. Physiol. Rev., 34: 608, 1954

140 VILLASANTE, J. G., JIMÉNEZ DÍAZ, C., DE LA BARREDA, P., MOLINA, A. F., and NUNO, J. Enzymic activities of the arterial wall and their modification by epinephrine, norepinephrine and vagal excitation. Bull. Inst med. Res. Univ. Madr., 7: 17, 1954.

141 VON BEZOLD, A., and HIRT, L. Über die physiologischen Wirkungen des essigsauren Veratrins. Untersuch. Physiol. Lab., Würzburg, 1: 73, 1867.

142 WALLACE, J., and SHARPEY-SCHAFER, E. P. Blood changes following controlled haemorrhage in man. Lancet, 2: 393, 1941.

143 WARREN, J. V., BRANNON, E. S., STEAD, E. A., Jr., and MERRILL, A J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances J. clin Invest., 24: 337, 1945.

144 WATERFIELD, R. L. The effects of posture on the circulating blood volume J. Physiol (Lond.), 72: 110, 1931.

145 WEISS, S, and BAKER, J. P. The carotid sinus reflex in health and disease — Its role in the causation of fainting and convulsions. Medicine (Baltimore), 12: 297, 1933.

146 WELLS, J. A, and RALL, D. P. The influence of N-(2 Bromoethyl)-N-ethyl-1-naphthalene-methylamine on the vasopressor responses of a series of amines. Fed Proc., 7: 264, 1948

147 WEST, G B The vasodepressor action of noradrenaline Brit J. Pharmacol., 4: 63, 1949.

148 WHITE, J. C., OKELBERRY, A. M., and WHITELAW, G. P. Vasomotor tonus of the denervated artery — Control of sympathectomized blood vessels by sympathomimetic hormones and its relation to the surgical treatment of patients with Raynaud's disease Arch Neurol. Psychiat. (Chicago), 36: 1251, 1936

149 WHITTAKER, S R F., and WINTON, F. R. The apparent viscosity of blood flowing in the isolated hindlimbs of the dog, and its variation with corpuscular concentration. J. Physiol. (Lond.), 78: 339, 1933

150 WILKINS, R. W, and EICHNA, L. W. Blood flow to the forearm and calf. I. Vasomotor reactions· Role of the sympathetic nervous system. Bull. Johns. Hopk. Hosp., 68. 425, 1941.

151 WINDESHEIM, J H, ROTH, G. M., and HINES, E A, Jr Direct arterial study of the blood pressure response to cold of normotensive subjects and patients with essential hypertension before and during treatment with various antihypertensive drugs Circulation (N Y.), 11: 878, 1955

152 WOLF, S., and HARDY, J. D. Studies on pain — Observations on pain due to local cooling and on factors involved in "cold pressor" effect. J. clin. Invest, 20: 521, 1941.

153 WOLFF, H. H. The mechanism and significance of the cold pressor response. Quart J Med, 20· 261, 1951

CHAPTER IX

# EXPERIMENTAL HYPERTENSION

## EXPERIMENTAL HYPERTENSION, PRIMARILY OF RENAL ORIGIN

A century of experiment and speculation intervened between Richard Bright and Harry Goldblatt. The decisive experiments of Goldblatt and his co-workers demonstrated the existence of a renal form of hypertension in which the release of pressor substances into the circulation could be demonstrated. The hypertension was induced in many animals and by various methods which involved interference with the renal circulation, and which were usually associated with renal ischaemia. In the century preceding Goldblatt there was no lack of recognition of the fact that renal hypertension could be induced experimentally. The importance of the work of Tigerstedt and Bergmann (1898) was widely recognized. There were many confirmations of their observation that intravenous injections of fresh extracts of kidney caused blood pressure increases, whereas extracts of other organs (adrenal and pituitary excepted) had no important hypertensive effect. That renin from the kidneys might explain the rises of blood pressure in experimental and in some forms of clinical hypertension was a favoured hypothesis which then, as now, lacked the full force of demonstration. Before Goldblatt, however, the relationship between interference with the kidney circulation and the release of renin into the blood stream was not generally recognized. A few writers had made experiments with renal ischaemia and obtained results which were qualitatively simil[illegible]
rises were often small. [illegible]
convincing blood press[illegible]
artery branch with removal of the opposite kidney.

Some early experiments with renal hypertension were directed to a comparison of the effects of ligature of one or both ureters with the effects of removing one or both kidneys. Hartwich (1930) showed that whereas in the short time available before death, only small blood pressure rises might be observed following bilateral nephrectomy, yet when the kidneys were left *in situ*, but with the ureters ligated, substantial blood pressure rises might occur. The extent to which waste products accumulated after bilateral nephrectomy and after bilateral ureteric ligature were very similar. Many early experiments

indicated that when the damaged kidneys were left *in situ*, substances from them were absorbed into the circulation and led to blood pressure elevation. This idea received support from Dicker (1938) who found that the hypertension following bilateral ureteric ligation was relieved when ligatures were applied also to the renal arteries; presumably the hypertensive substances no longer entered the circulation.

Blood pressure elevation had also been observed following the partial or complete obstruction of one or, with more effect, both renal veins (Dicker, 1938). Experiments in which a renal artery was tied completely, or both renal arteries were tied, were associated with rises of blood pressure, and these findings were contrasted with the comparatively slight changes in blood pressure which occurred when the kidneys were removed (Dicker, 1938).

### Hypertension Following the Narrowing of Renal Arteries (Goldblatt)

Goldblatt, Lynch, Hanzal and Summerville (1934) induced renal ischaemia by an adjustable silver clamp placed on the renal arteries of dogs. The blood pressure could be raised moderately, or to considerable heights, depending on the degree of ischaemia, and at the time of reporting, hypertension had lasted for periods as long as fifteen months. In some dogs the blood pressure rise occurred without obvious impairment in the urinary excretions.

These observations were soon confirmed by Page (1935) who noted that renal denervation did not prevent the blood pressure rise. Goldblatt (1937) showed that hypertension could be produced in the macaque monkey by renal artery constriction and Goldblatt, Kahn and Lewis (1943) obtained the same results in sheep and goats Pickering and Prinzmetal (1938) used rabbits and described a very simple silver clip which could be used to narrow the renal arteries to a desired degree. They noted the effect of narrowing one renal artery was much less than the effect of narrowing both. It was of interest that the rise of pressure might take a month or more to become complete. The induced hypertension was associated with hypertrophy of the heart. These authors [144], using a standard reference powder, suggested a method of bioassay for renin in terms of its action upon the blood pressure of the unanaesthetized rabbit. They found, confirming Tigerstedt and Bergmann (1898), that the renin is present in the cortex but not in the medulla. Glenn, Child and Heuer (1938) transplanted a kidney to the neck and then removed the dog's remaining kidney. They found that constriction of the artery of the transplanted kidney caused a blood pressure rise which could not be attributed to any stimulation of renal nerves. Houssay and Fasciolo (1938) also used the transplanted kidney, and found that when an ischaemic kidney is removed from a hypertensive dog and grafted

to the neck of a normotensive dog then the blood pressure rises more rapidly in the recipient animal than it did originally in the donor. Verney and Vogt (1944) showed in unanaesthetized dogs that when the renal artery of a sole remaining kidney is constricted by a special compression unit the blood pressure is rising some 8 to 18 minutes later.

Wilson and Pickering (1938) showed that high degrees of renal constriction in rabbits may lead to changes in the small arteries, and arterioles, resembling those seen in human malignant hypertension. Those lesions, including medial necrosis, were reported in the blood

peripheral to the clip was protected against the high blood pressure; and that the high blood pressure was the most significant factor responsible for these histological changes. Wilson and Byrom (1939) were able to produce a sustained hypertension in rats by partial occlusion of one renal artery. They noted that although the kidney with the clipped artery was protected, the untouched kidney exposed to the full effect of the hypertension exhibited histological changes similar to those of malignant hypertension in man. They considered that these changes were due to the hypertension and not the result of renal failure. It was suggested that a vicious circle might be set up in which the renal lesion caused hypertension, and the hypertension then induced further renal lesions

Goldblatt, Kahn and Hanzal (1939) showed that constriction of the abdominal aorta above the renal arteries in dogs gave rise to hypertension, but constriction below the renal arteries did not do so. When constriction above the renal arteries was severe, the hypertension was usually fatal, and blood vessels exhibited histological changes similar to those of malignant hypertension in man. Rytand (1938) induced hypertension in rats by constriction of the aorta. Cardiac hypertrophy was used as an indication of hypertension. There has been much dispute as to whether the hypertension of clinical and of experimental aortic coarctation results from mechanical obstruction, from renal ischaemia or from some [illegible]

Kohlstaedt [illegible]

the isolated d[illegible] with defibrinated blood released renin into the perfusate when the pulse pressure was reduced. There was a slight decrease of blood flow in most experiments but the authors laid greater stress on the importance of the diminished pulsation.

Fasciolo, Houssay and Taquini (1938) found that normal kidney tissue diminishes the blood pressure raising action of ischaemic kidneys Rodbard and Katz (1941) found that the renal pressor

substance liberated from ischaemic kidneys is destroyed by normal kidneys.

### Angiotonin (Hypertensin) and its Precursors

Between 1938 and 1940 a series of experiments were in progress in Argentine and in U.S.A. which showed that renin, by an enzymatic action upon a plasma substrate, gave rise to the formation of a new heat-stable, dialyzable substance with a short pressor action. Braun-Menéndez, Fasciolo, Leloir and Muñoz (1939, 1940) found this new pressor substance, which they called hypertensin, in the plasma of venous blood from kidneys with acute ischaemia and recognized it to be different from renin. They were led to incubate renin with blood serum and a pressor substance was formed identical with the substance which they had extracted from the renal vein blood.

Kohlstaedt, Helmer and Page (1938), in the United States found that, while purified renin gave a blood pressure rise when injected into whole animals, it did not cause vaso-constriction when it was dissolved in Ringer's solution and perfused through the blood vessels of a dog's tail. If, however, dog's whole blood was added to the purified renin the mixture caused strong vaso-constriction in the perfused dog's tail. They found (Kohlstaedt, Page and Helmer, 1940) that the plasma proteins contained an 'activator' of renin. It seems to be generally agreed that the pressor action of pure renin is due to a new substance which is formed when renin acts on this plasma substrate which was called 'hypertensinogen' by the South Americans and 'renin activator' by the United States workers. Page and his co-workers called the new pressor substance angiotonin, which substance is identical with the hypertensin of the South American workers. The rapid disappearance of angiotonin from blood proved to be due to destruction or inactivation by an enzyme-like substance, angiotonase (or hypertensinase) (Braun-Menéndez, Fasciolo, Leloir and Muñoz, 1939; Page and Helmer, 1940; Leloir, Muñoz, Braun-Menéndez and Fasciolo, 1940). For further detail and literature the excellent monograph by Braun-Menéndez and his co-workers (1946) should be consulted.

The detection of renin and of hypertensin in the circulating blood is a matter of great technical difficulty but Gollan, Richardson and Goldblatt (1948) and Kahn, Skeggs and Shumway (1950) considered that they had demonstrated hypertensin in the systemic blood of animals with experimental malignant renal hypertension. The latter authors obtained the hypertensin by dialysis, using an artificial kidney. The amount of circulating hypertensin obtained in this way was not very different in normal and malignant hypertensive dogs, but the substance was absent from the blood of dogs after bilateral nephrectomy.

Hill and Pickering (1939) and Blacket et al., (1950) found that it

was possible to maintain hypertension in rabbits by the continuous infusion of renin. They felt that this gave support to the view that the hypertension following constriction of the renal arteries is due to the release of renin. Taggart and Drury (1940) were unable by renin infusion to produce hypertension of a degree which was comparable with the degree of hypertension which can be induced by constriction of the renal arteries in rabbits. They also pointed out that the rise of the blood pressure for each increment of the dose of renin becomes less as the dose is increased, therefore they argue, had the elevation in the blood pressure been due to renin, the blood pressure rise in the hypertensive animal following a dose of renin should have been smaller than in a normotensive animal. This, however, was not the case.

Renin and angiotonin are difficult to isolate, but in states approaching purity both substances exhibit a high degree of activity. Their high potency lends support to the view that their presence in animals with experimental hypertension is not purely coincidental.

Increase in the reactivity of blood vessels to pressor stimuli may be concerned in clipped kidney [illegible] and McQuee [illegible] from rats wi [illegible] exhibit an e [illegible] blood vessels from control rats with both kidneys intact (Fig. IX 1). The same result is obtained with blood vessels from rats with one kidney clipped and the [illegible] kidney intact, must be attributed to something coming from the clipped kidney.

## Other Pressor Substances from the Kidneys in Experimental Renal Hypertension

*VEM*. Shorr (1950) has summarized his work on a vaso-excitor material (VEM) of renal origin which was done in conjunction with Zweifach and others [164, 166]. The substance is detected by its effect on the vessels of the meso-appendix of the rat, which by its action become sensitized to the vasoconstricting action of adrenaline. Shorr states that 30 minutes after the application of a Goldblatt clamp, VEM can be detected in the renal vein blood. The VEM is present during the acute stage of renal hypertension but assays of the VEM in chronic renal hypertension reveal a decrease in the VEM activity. Shorr describes experiments suggesting that this apparent decrease in the titre of VEM is due to the [illegible] (vaso-depressor material [illegible] incubation with normal [illegible] VDM activity. VDM has been identified as ferritin. It should be pointed out that

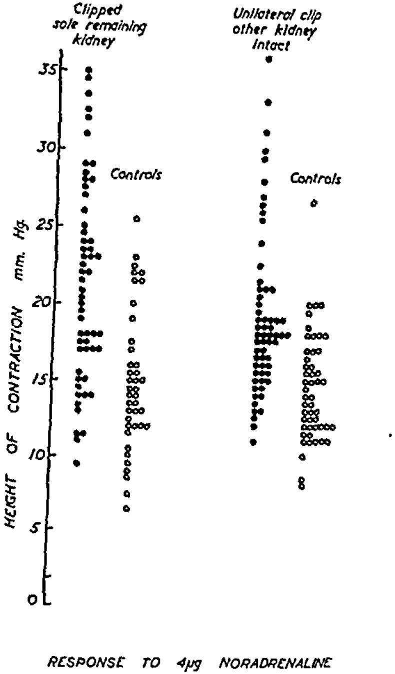



Fig. IX 1

Reactivity of perfused rat blood vessels to injections of noradrenaline. The blood vessels of the lower limbs of the rat were perfused at constant rate through the aorta. Changes in the height of the perfusion pressure were recorded

*Left.* Preparations of limb blood vessels from rats with a clipped sole remaining kidney were compared with corresponding blood vessels from control rats with untouched kidneys. Blood vessels from rats with a sole remaining clipped kidney were more reactive to noradrenaline than the blood vessels of control rats

*Right.* The experiment was repeated clipping one kidney but leaving the animal's other kidney intact. Blood vessels from rats with one clipped kidney and one kidney intact were more reactive to noradrenaline than the blood vessels of control rats.

VDM does not cause direct constriction of blood vessels, nor is VDM depressor. The rat meso-appendix is a very sensitive preparation and it is uncertain whether these substances have any part to play in the blood pressure elevation of experimental renal hypertension.

*Sustained pressor principle.* — Shipley, Helmer and Kohlstaedt (1947) described a principle which is released into the blood stream when either the blood flow to or the blood pressure within the kidneys is diminished. Apparently the blood pressure elevation in nephrectomized animals after injection of the material may be more prolonged than it is after renin. There has been, however, great difficulty in separating the sustained principle from renin, since both appear in the venous plasma of ischaemic kidneys. Following the injection of crude kidney extracts into animals, sera can be obtained with an anti-body titre which is high, both for renin and for sustained pressor principle. The possibility has not yet been excluded that sustained pressor principle and renin are identical or in a slightly different physical state.

*Pherentasin.* — Practically all the work on Pherentasin has been carried out in man and will be described in Chapter XI.

*Pressor amines.* — An interesting possibility was raised by Bing and Zucker (1941) who noted that kidneys with normal blood flows failed to change DOPA (l-dihydroxyphenyl alanine) into a pressor amine whereas completely or severely ischaemic kidneys do this. In their experiments the DOPA was injected through the aorta into the left kidney or sometimes into the renal parenchyma. There is no definite evidence, however, of pressor amine formation in the absence of DOPA injections.

## Additional Factors Concerned in Experimental Renal Hypertension

About 1940 it seemed as though the Goldblatt mechanism provided a sufficient expl...

tho

... (1942) used their method of bio-assay to determine the renin content of rabbit kidneys in the first 8 days after inducing substantial renal ischaemia; they noted an increase in the amount of renin above the normal. When, however, hypertension had been in progress for 2 to 17 months they found the renin content had returned to normal Renin injected into the blood stream could be bio-assayed 10 to 15 minutes after ... was not found ...

2 to

tensi... hyper-

...aemia was due to the release of renin into

the blood stream but raised the question of whether other factors might take over at a later stage. Ogden (1947) found that in the rat, after a period of experimental renal hypertension lasting 2 weeks, the effect upon the blood pressure of sodium phenobarbitone, sodium pentobarbitone, yohimbine or 883F. was increased. This finding seemed to favour the view that after a period of time the nervous system takes over from some initial humoral mechanism. Pickering (1945) studied the effect of inducing a Goldblatt type of hypertension, by constriction of the renal artery of a kidney, in rabbits which had already been subjected to unilateral nephrectomy. He found that when hypertension was produced by narrowing the renal artery of the *only remaining* kidney, then the removal of this kidney within the first 8 days after narrowing of its renal artery, abolished hypertension within a few hours. If, however, the hypertension were allowed to continue for 7 weeks, *then removal of the sole remaining kidney caused no important fall in the blood pressure during the 4 days' survival period. He showed* that the animals so treated were still capable of inactivating renin. It would seem, therefore, that after a period of time the hypertension can be maintained by some non-renal factor. This observation has been made in rats by Restall (1949) and Floyer (1951), in rabbits by Fleming (1949 and 1953), Blacket and Sellers (1951) and Daniel et al. (1954); and in dogs by Grollman (1946), Shipley, Helmer and Kohlstaedt (1947) and Oppenheimer et al. (1952). There is little doubt that if an experimental hypertension, induced by renal ischaemia has been allowed to persist in the rat or in the rabbit then skilful removal of the remaining kidney does not abolish the hypertension during the few days in which the animal survives the procedure; and the hypertension persists longer if survival is extended by special dietary methods or by *in vivo* dialysis. Without doubt there is something which can maintain the blood pressure level in the absence of kidneys, but Muirhead, Vanatta and Grollman (1949) Grollman and Halpert (1949) and Muirhead, Grollman and Vanatta (1950) have pointed out that the interpretation of such experiments is far from simple, as bilateral nephrectomy and possibly unilateral nephrectomy may raise the blood pressure level even in the absence of previous experimental hypertension.

A fundamental experiment was made by Byrom and Dodson (1949) [illegible] persisted after removal of the ischaemic kidney, but it fell to normal when the clip obstructing the renal artery was removed. This observation has been confirmed by Blacket and Sellers (1951) and by Floyer (1951) (see Fig. IX 2). It is evident that the preservation of additional non-ischaemic renal tissue in the body has had the effect of reducing the blood pressure. It is not clear whether the ischaemic kidney

was supplying a pressor agent or whether, on removal of the clip, the ... pressor ... al of the ... e hyper-

tension.

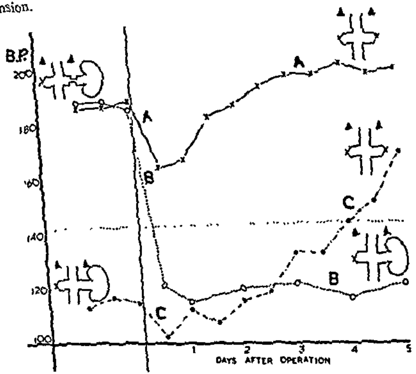



Fig. IX 2

Changes in the mean blood pressure of three groups of rats.
A (x— — — — — —x) With experimental renal hypertension subjected to total nephrectomy
B (o— — — — —o) With experimental renal hypertension in which clip was removed
C (●— —.— — — ●) Normal rats subjected to total nephr...
The horizontal dotted line dr... the upper limit of normal blo... paper (3) (Floyer, M A Cl...

## Effect of Decrease in the Amount of Renal Tissue - Including Bilateral Nephrectomy

Fasciolo, Houssay and Taquini (1938) Katz, ... Friedman (1938) and Katz, Fr... obtained evidence that the pre... tended to antagonize, in some mysterious way the pressor ... an ischaemic ...

to renal pressor substances. Grollman (1944b) has laid great stress on this protective renal mechanism and considers that absence of a protective action of the kidneys is the main factor responsible for blood pressure elevation in experimental renal hypertension, which he regards as essentially of the same nature as the hypertension which occurs, under certain conditions, after bilateral nephrectomy. He grants the probability that pressor substances are released under conditions of acute ischaemia.

Braun-Menéndez (1952) has made an interesting study of the relationship between renal weight and body weight in the course of a number of experimental procedures which raise or lower the blood pressure by a renal mechanism. He proposes the hypothesis that a substance or substances (renotropin), under the influence of anterior pituitary and thyroid hormones, is responsible for hypertrophy of the kidney in response to the body needs. When the remaining renal tissue is unable to respond to the stimulus of renotropin, hypertension results.

Floyer (1955) also has made a series of instructive experiments on renoprival hypertension in rats. He has shown that the kidney antagonizes renoprival hypertension, even when its excretory function is abolished by inserting the cut end of the ureter into the inferior vena cava. He thinks there is no long-lasting secretion of pressor substances by ischaemic kidneys; but the circulatory change induced by clipping a renal artery leads to a form of hypertension which is basically similar to that of renoprival hypertension, depending upon loss of the capacity to inhibit an extrarenal pressor mechanism (Fig. IX 2).

Interpretation of the effects of bilateral nephrectomy is difficult. In the bilaterally nephrectomized animal there is retention of substances which are normally excreted, and a disturbance of water and electrolyte balance, and the blood volume may change. These and other factors exercise a strong influence on the blood pressure level following nephrectomy. *In vivo* dialysis, while prolonging life, needs most careful control of electrolyte balance.

It does not always happen that bilateral nephrectomy leads to an elevation of the blood pressure during the short time in which animals ordinarily survive this operation (Backman, 1916; Dicker, 1938). Hartwich (1930) reported slight blood pressure rises, and Braun-Menéndez and Von Euler (1947) obtained a degree of hypertension in 33 per cent of bilaterally nephrectomized rats. Important progress has followed the development of methods of keeping bilaterally nephrectomized animals alive by the artificial kidney and by peritoneal lavage. Many papers have been published showing that hypertension may develop in bilaterally nephrectomized animals, kept alive for some weeks. By such procedures Grollman, Muirhead and Vanatta

(1949) obtained hypertension in bilaterally nephrectomized dogs. At autopsy pathological changes characteristic of malignant hypertension were found.

*Effect of salt and water intake on the blood pressure after bilateral nephrectomy.* — It soon became evident that after bilateral nephrectomy the degree of hydration and of salt retention played an important part in deciding if high blood pressure would develop.
Where salt and water were retained the blood pressure tended to be increased (Braun-Menéndez and Covian, 1948; Orbison et al., 1952). On the other hand, if the salt and water reserves of the dogs were decreased or prevented from rising there was ordinarily no development of hypertension (Leonards and Heisler, 1951, 1952). Houck (1954) showed that bilaterally nephrectomized dogs could be prevented from developing hypertension if they were dehydrated and failed to gain in extra-cellular fluid volume; they became hypertensive if allowed to accumulate salt and water, and could once more have their blood pressures reduced by dehydration. He concluded, however, that a maintained increase in body fluids is not necessary to maintain hypertension Muirhead, Fogelman, Jones and Graham (1953) were of the opinion that significant hypertension could occur in dogs maintained by dialysis, even in the absence of an increase in the extracellular fluid or demonstrable sodium excess. Grollman (1953) believes that hypertension develops in bilaterally nephrectomized dogs if the volume and composition of the extracellular fluid are within normal limits.

Tobia[illegible]
of the [illegible]
before [illegible] contains sodium salts. If sodium were withheld from the diets only 1 out of 51 rats developed hypertension following bilateral nephrectomy. Likewise, it did not occur if the adrenals were removed.

Grollman and Shapiro (1953) report an increase in the extracellular space in essential hypertension as compared with the normal, and also in hypertensive dogs as compared with normotensive dogs. Muirhead, Jones and Graham (1953) found that, following bilateral nephrectomy in the dog, they were able to obtain hypertension without an exogenous sodium load and in the absence of expansion of the extracellular fluid volume There was even a decrease in the blood volume at the time the blood pressure was elevated The authors agree with others that the blood pressure elevation is potentiated by the addition of salt. They thought that dietary protein [illegible]

Grollman, [illegible]
is deprived of [illegible]
gut then the animal remained normoten[illegible]
means of the artificial kidne[illegible]

pressure rose. They conclude that the kidney ordinarily has an incretory function, independent of its excretory activities. The lack of incretory activity results in hypertension.

There is evidence throughout the literature that bilateral nephrectomy alone sometimes gives rise to hypertension, even when there is no peritoneal dialysis or use of artificial kidney. This occurs particularly when the animals do not lose salt by vomiting.

There has been a growing feeling that chronic clipped kidney hypertension and renoprival hypertension had much in common, and might even be due to an identical mechanism. Against this is an interesting observation by Kolff and Page (1955) that antirenin did not prevent the development of renoprival hypertension in dogs but abolished the pressor response to renin.

McQueen and Veale (1955) have shown in perfusion experiments that the blood vessels from bilaterally nephrectomized rats are more sensitive to the vasoconstriction of noradrenaline than the blood vessels of control rats. This hypersensitivity is lost if the bilaterally nephrectomized rat has both adrenal glands removed, but is demonstrable if the adrenalectomized animals are given extra salt. This work shows that there are vascular reactions which do not depend upon the blood volume changes which make the interpretation of whole animal experiments so difficult after bilateral nephrectomy.

*Effect of bilateral nephrectomy in one of a pair of parabiotic rats.*—Grollman and Rule (1943) showed that the nephrectomized member of a pair of parabiotic rats was commonly hypertensive though the other member of the pair would ordinarily have a normal blood pressure. Similar results were obtained by Ledingham (1951) and by Turiaf et al. (1954).

## Alternative Methods of Inducing Experimental Renal Hypertension

Several methods of inducing experimental renal hypertension have been suggested which depend in common upon some form of interference with the renal circulation. Page (1939) induced persistent arterial hypertension by enveloping the kidneys in cellophane or in silk. This led to perinephritis with the formation of a fibrous constricting hull. A similar method has been used by many authors. Abrams and Sobin (1947) prepared latex rubber capsules of a shape similar to the shape of the kidneys, which were slipped on over the external surface of the kidneys at operation These they found were an effective and simple means of inducing hypertension in large numbers of rats. Rau (1950) sprayed a plastic solution on the external surface of the kidney. This also gave rise to hypertension as the result of perinephritis. Dr. McQueen kindly undertook to test out this plastic

spray method of inducing hypertension and initial results suggest that it is a useful procedure.

Grollman (1944a) applied a figure-of-eight ligature around the kidneys and prefers this to the use of cellophane or silk. He has used umbilical tape and applied it to the kidneys in rabbits, dogs, and rats.

Fibrosis of the kidneys induced by x-ray radiation has been shown by Hartman, Bolliger and Doub (1927) to cause blood pressure elevation. The kidneys show thickening of the blood vessels and often a substantial endarteritis. It is interesting that animals with a marked increase in the blood pressure showed retinal changes, including haemorrhages. Hartman, Bolliger and Doub (1926) also found that cardiac hypertrophy developed together with left ventricular preponderance on the electrocardiograms. A confirmation of these results comes from Zollinger (1952).

### Haemodynamics in Renal Hypertension

The application of a clamp to the renal artery seems to be a very simple procedure which may be expected to cause decrease in the pressure beyond the clamp with a decrease in the renal blood flow. The apparent simplicity, however, is deceptive. Application of the clamp is commonly followed by elevation of the blood pressure so that although the renal artery is narrowed, the rise in perfusion [illegible] for this to some degree However [illegible] to be a decrease in the amount [illegible] tion in the flow through the ki[illegible] cases of renal hypertension th[illegible]

[illegible] Macy Conference, concurred with this view and stated that the direct renal arterial pressure distal to the clamp in chronic renal hypertension [illegible] [illegible] then summed up the changes in renal haemodynamics which occur as being reduction in the pulse pressure, varying degrees of cortical hypoxia, and a degree of acidification of the periphery of the renal cortex.

## COMMENT ON EXPERIMENTAL MALIGNANT HYPERTENSION

Local death of a part of the arterial wall gives rise to an appearance described as arteriolonecrosis, which is the most characteristic histological appearance of malignant hypertension [illegible] clinically. It is clear that [illegible]

in some of the more severe examples of experimental renal hypertension, usually those with greater narrowing of the renal arteries (Goldblatt, 1938). It is probable on clinical and experimental evidence that the level of the blood pressure is concerned in some important way in its production.

Wilson and Pickering (1938) using rabbits, Wilson and Byrom (1939) using rats, and Byrom and Dodson (1948) using rats, induced hypertension of the malignant type by renal ischaemia. The relationship between the presence of lesions and the height of the blood pressure, together with the absence of serious lesions in the protected ischaemic kidneys, persuaded them that hypertension was the chief cause for the lesions. Goldblatt (1947), however, considers that hypertension alone is not sufficient to explain the development of arteriolar necrosis. He believes that the rats which developed malignant changes with unilateral renal ischaemia must have started with some renal impairment from pyelonephritis such as is common in some rat colonies and that the occurrence of malignant hypertension changes after unilateral renal ischaemia is confined to the rat.

In this connection it is now generally agreed that some of the characteristic clinical features of malignant hypertension can be reversed or lessened to an important extent in man by a sufficient reduction of the blood pressure. This may be merely a reflection in clinical material of the observation that the lesions are intensified by hypertension. On the other hand, it may be that causes which are responsible for the arteriolar necrosis in hypertension are enhanced by the blood pressure elevation and, when the blood pressure falls, their activity is reduced to below a threshold value, so the lesions are no longer manifest. Recently Hopkins et al. (1956) have shown that experimental malignant hypertension in the dog is usually accompanied by extensive vascular damage (including necrosis) in the ileum. When, however, the artery supplying an isolated segment of the ileum is narrowed by a clamp, the segment, now protected from the high arterial pressure by the clamp, shows no arteriolonecrosis.

Fleming (1953) made some interesting experiments with rabbits rendered severely hypertensive by the application of a clip on a renal artery following removal of the other kidney. He studied the histology of 9 rabbits dying with uraemia, noting the appearances of malignant hypertension. He compared the histology of these animals with that of 10 rabbits similarly treated, with correspondingly high blood pressures, but in which the terminal uraemia did not occur spontaneously being induced by the removal of the remaining ischaemic kidney. The blood pressures in these nephrectomized animals remained high until death and the nonprotein nitrogens rose to high levels, yet in contrast with the animals that died spontaneously, these animals exhibited none of the histological features of malignant hypertension. It should be noted

that no special means were taken to maintain these animals alive for long periods of time by methods such as peritoneal lavage or artificial kidney. This observation has been confirmed by Daniel et al. (1951b). In the height of the blood pressure, and in the terminal degree of nitrogen retention, the two groups were very similar. While lack of renal tissue has been offered as an explanation for the failure to exhibit

Byrom (1937) gave large injections of vasopressin to rats and found that it led to vascular lesions which resembled malignant hypertension in man. The doses amounted to 5—40 units subcutaneously daily or twice daily for several weeks. Blood pressure rises and constriction of blood vessels occurred.

Grimson (1949) pointed out that it was general experience that animals with neurogenic hypertension due to the section of buffer nerves did not develop malignant hypertension as judged by retinitis and other manifestations.

Muirhead et al. (1953) studied the lesions which occur in several

was present in many of the animals but the lesions occurred also in some of the animals not exhibiting hypertension. The lesions in the heart were not dependent upon lesions in the coronary vessels: in other words, there was some direct damage. The arterial lesions were mainly necrosis and degeneration of the smooth muscle of the media, and were observed in 35 per cent of the 17 animals without hypertension in 45 per cent of the 9 [illegible]

cent of 31 animals [illegible]

also observed in [illegible]

Muirhead, et a[illegible]

malignant hypert[illegible] following manipulations such as the ligation of both ureters, the ligation of one ureter followed by removal of the opposite kidney, the implantation of the ureter into the small bowel followed by contralateral nephrectomy, the implantation of the ureter into the inferior vena cava and contralateral nephrectomy, and the sectioning of both ureters so as to permit the free flow of urine into the peritoneal cavity."

There seems to be good evidence that certain experimental procedures may lead even to very rapid production of [illegible]

picture [illegible]

times wi[illegible]

however [illegible]

It must be remembered that the histological picture of arteriolar

necrosis merely represents local death of a part of the wall of an arteriole. There seems to be no justification for believing that all such lesions have a common origin. It seems reasonable to suppose that the effects of a variety of adverse influences might summate, leading to arteriolar necrosis when acting in combination, but not doing so when acting singly.

## PROCEDURES WHICH MAY MODIFY EXPERIMENTAL RENAL HYPERTENSION

### Effect of Salt Depletion

Hantschmann (1931) and Grollman and Harrison (1945) showed that rigid salt restriction decreases and salt administration increases slightly the blood pressure in animals with experimental renal hypertension. Hantschmann's experiments were on dogs, those of Grollman and Harrison were made on rats. Frieden, Stamler, Hwang, Kuramoto and Katz (1951) found that in benign Goldblatt hypertension the blood pressure was not reduced by a low sodium diet, but a low sodium diet when combined with further salt depletion by peritoneal lavage reduced the blood pressure to normotensive levels. There was also a rise in the haematocrit readings, suggesting decrease of blood volume.

### Effect of Adrenalectomy

It is generally recognized that adrenalectomy, performed before or subsequent to narrowing of renal blood vessels, usually reduces the height of the blood pressure. In general it is found that injection of adrenal cortex hormones and salt administration cause recurrence of the blood pressure increase (Page, 1938; Collins and Wood, 1938). Secker (1940) noted that stimulation of the central end of a sciatic nerve in adrenalectomized cats, when repeated, gave rise to blood pressure rises of declining magnitude. The response returns to normal when an active cortical extract is administered. Cleghorn, et al. (1950) found that, after bilateral adrenalectomy, some degree of vascular insensitivity to pressor stimuli such as adrenaline, nicotine, barium and pitressin persisted after adrenalectomy even though cortical adrenal hormones were administered subsequently

### Effect of Hypophysectomy

Hypophysectomy has been shown by Page and Sweet (1937) to reduce the blood pressure in experimental renal hypertension in dogs. It is possible that hypophysectomy influences the blood pressure, in part at least, by diminishing the secretion of the adrenal cortex.

## Effect of Pregnancy

Pregnancy in the course of experimental hypertension in rabbits has been associated with falls in the blood pressure (Corbit, 1941). Normal rabbits also have a blood pressure fall towards the end of pregnancy. Dill and Erickson (1941) find, however, that the adverse effects of renal ischaemia in rabbits, such as myocardial necrosis, are accentuated when the rabbits are pregnant.

## Effect of Extirpation of or Damage to the Liver

There is some evidence that the development of experimental hypertension is influenced by the liver. Davis et al. (1949) found a slight fall in the blood pressure of Goldblatt dogs after narrowing of the hepatic arteries and portal veins. They had the impression that the pathological changes in the liver might diminish the formation of hypertensinogen. Page (1950) made experiments in which the liver was removed and found it rendered blood vessels much less sensitive to a number of pressor stimuli including barium, renin and to some extent angiotonin and pitressin.

## Effect of Operations to Improve the Renal Circulation

In lower animals successful attempts have been made to improve the renal circulation by splenorenopexy (Weeks et al. 1940; and Cerqua and Samaan, 1939). It seems that in small animals the collateral circulation which forms is often sufficient to lower the blood pressure [illegible]

[illegible] not been successful.

## Effect of Pyrogens

Stamler, Rodbard, Katz and Fishman (1949) found that tissue injury, particularly abscess formation, induced a sustained fall in the blood pressure in some dogs with experimental renal hypertension and also in some [illegible]
evidence that [illegible]
pheral resista[illegible] substances such as turpentine induced a fall in the blood pressure indicating that the response is not a specific one.

## The Modification of Experimental Hypertension by Immunological Means

The occurrence of non-specific effects such as those induced by pyrogens rendered the investigations of Wakerlin a most difficult undertaking. In a situation of great complexity Wakerlin and his collaborators (1950) have succeeded in establishing that anti-renins are produced in dogs receiving hog renin injection. They found that

hog renin produced from cortex, and excluding the medulla, produced much more reliable results.

Injections of hog-cortex renin into dogs with recent or long-standing hypertension led to blood pressure falls, and there was a strong correlation between anti-hypertensive effects and the antirenin titre of the recipient dog's serum.

These results have been confirmed by Goldblatt and co-workers and by Helmer and co-workers (in a personal communication to Wakerlin). Wakerlin found that his crude hog renin prepared from the cortex had a protective action against the arteriolonecrotic lesions characteristic of experimental malignant hypertension. This protection did not seem to be dependent upon anti-hypertensive effects. Burns and Wakerlin (1953) offer a number of possible explanations for this phenomenon, the further investigation of which may clarify the relationship between high blood pressure and the appearance of histological changes characteristic of the malignant hypertension of experimental animals Unfortunately various animal renins vary in their properties, and up to the present time it has not been possible to prepare any anti-human renin which would assist in the investigation of whether the renin-angiotonin system operates in certain forms of renal hypertension in man. In view of the differences between acute and chronic hypertension from renal ischaemia it is of very great interest that Wakerlin found that hog-cortex renin injections led to decrease of blood pressure in both acute and chronic experimental renal hypertension.

## The Modification of Experimental Hypertension by Nervous Means

Several authors have shown that denervation of the kidneys does not prevent the development of experimental renal hypertension, nor does the blood pressure fall to any extent if the kidneys are denervated after the hypertension is established (Collins, 1936; Page, 1935; Heymans et al. 1937). Likewise there is general agreement that in experimental renal hypertension small temporary falls of blood pressure may occur following sympathectomy, of varying degrees of completeness, but the main blood pressure elevation persists (Goldblatt, Gross and Hanzal, 1937; Freeman and Page, 1937; Alpert, Alving and Grimson, 1937). Houck (1956) has shown that total sympathectomy in dogs does not prevent the development of renoprival hypertension.

Goldblatt and Wartman (1937) found that anterior spinal nerve root section did not interfere with the development of experimental hypertension. On the other hand Dock (1940) found that pithing abolished the vasoconstriction in renal hypertension It is possible that this is due to the release of products decreasing the activity of blood vessels.

Nickerson et al. (1948) observed the effect of peripheral sympathetic blockade by Dibenamine in experimental renal hypertension and thought that in rats the neurogenic factor so assessed was no greater in late than in early hypertension.

### Various other Procedures which may Modify the Blood Pressure Level in Experimental Renal Hypertension

Schroeder and Adams (1941) studied the effect of tyrosinase from mushrooms on experimental renal hypertension. They reported that intravenous injection of the tyrosinase lowered the blood pressure; and that angiotonin, renin, adrenaline and tyramine were inactivated *in vitro* by the substance.

The effect of high protein diets on dogs with experimental renal hypertension was studied by Phillipsborn et al. (1941) who found blood pressure rises from the diet were encountered exceptionally and only in dogs with a degree of excretory renal insufficiency.

An important type of experimental renal hypertension has been described by Hartroft (1948) and Best and Hartroft (1949). They noted that weanling rats when fed on choline-deficient diets develop renal damage which is associated with considerable blood pressure elevation.

It has been shown by [illegible] extracts reduces the [illegible] in experimental renal [illegible] infrequently causes a fall of blood pressure associated with the pyrogenic effect. Various bacterial substances, *e.g.* T.A.B., and extracts of tissues other than the kidney have the same action.

## EXPERIMENTAL HYPERTENSION, PRIMARILY OF NON-RENAL ORIGIN

For a circulatory stimulus to induce sustained hypertension it seems that either the stimulus must be sufficiently powerful to overcome the homeostatic control mechanisms, or the action of the [illegible] mechanisms [illegible] a [illegible] later stage in forms of experimental hypertension which, primarily, are of non-renal origin.

### Experimental Hypertension of Nervous Origin

It is common knowledge in experiments on conscious laboratory animals that nervousness and excitement give rise to elevations of the blood pressure, sometimes of considerable magnitude. Many corres-

ponding observations have been made in man to which reference is made elsewhere.

Sachs, Brendler and Fulton (1949) found that stimulation of the orbital gyri in the cat, dog and monkey gave rise to alterations in the blood pressure. The direction of blood pressure change depended to an important extent on the wave form of the electrical stimulation. Walter and Pijoan (1937) reported a number of large blood pressure rises in dogs which followed 3 mm. transverse incisions, immediately posterior to the infundibulum and deep enough to puncture the 3rd. ventricle. Many other writers have described blood pressure rises from stimulation of various parts of the brain, but for the most part the changes are temporary and small, and so far experiments of this kind do not appear to have evoked substantial responses even from the nervous mechanisms which, in other circumstances, are known to cause large rises of blood pressure.

*Hypertension from interference with the carotid sinus and aortic nerves.* — It was shown by Hering (1927) that section of the aortic nerves and denervation of the carotid sinus led to a rise in blood pressure in the rabbit; and similar results have been obtained in other animals, notably the dog. The characteristics of this form of hypertension have been reviewed by Heymans (1938 a and b). The blood pressure increase is associated with cardiac acceleration and increase of cardiac output (Bing, 1944). The blood pressure is exceedingly labile (Thomas, 1944). In dogs it commonly rises high when they are visited by the experimenter, and may fall away as they quieten down The blood pressure is much decreased, sometimes even to normal, by anaesthesia and during sleep (Grimson, Kernodle and Hill, 1944; Page and McCubbin, 1951). The casual blood pressures may rise to great heights; Thomas (1944) reported pressures as high as 425 systolic and 222 diastolic in dogs with neurogenic hypertension of five years' duration. All observers are agreed that animals withstand this form of hypertension much better than experimental renal hypertension The histological changes, when they occur, are milder and increases of heart size are less pronounced. One possible reason for this, not necessarily the only one, is the intermittent character of the blood pressure increase. Recently Dammin et al. (1956) have reported arteriolosclerotic lesions in 3 dogs with moderator nerve section and observed for 6, 7 and 7 years. The lesions appeared between 2 and 3½ years after hypertension was induced.

It seems to have been demonstrated that neurogenic hypertension as ordinarily produced by division of buffer nerves is labile and falls when the animal is at rest and unstimulated or under adequate sedation. Grimson (1949), however, expressed the view that neurogenic hypertension only fell towards normal levels at rest or under sedation when the denervation was inadequate He considered that even with

experience, he would be fortunate to obtain two persistent hypertensions out of five. The labile neurogenic hypertensives he regarded as due to inadequate denervation.

It was shown by Heymans and Bouckaert (1935, 1936) that total bilateral sympathectomy, from the cervical ganglion to the pelvic chain, cured neurogenic hypertension. In late years some interesting experiments have been made in which various vasoconstrictor and vasodilator drugs have been applied directly to the carotid sinus region. Blood pressure changes stimulate the carotid sinus region by deformation of the arterial wall and not by the direct effect of the drugs upon receptors. Consequently, the state of muscular tone of the arterial wall influences the response of the carotid sinus region, and it is found that the local application of vasoconstrictor agents leads to a fall in the blood pressure and of vasodilators to an increase. Recently Wakerlin and co-workers (1954) approached this subject in another way. They gave external support to the carotid sinus regions by application of plastic moulds devised to avoid injury to the nerves. The procedure led to an increase in the blood pressure. The result of this experiment is consistent with Volhard's suggestion (1931) that rigidity of the wall of the carotid sinus from arteriosclerotic changes may render the carotid sinus unresponsive to, and unable to antagonize, rises of pressure within it. Crandall and Wakerlin (1956) find that their carotid area hyperten-

... in some dogs when the internal and external (and occipital) arteries were constricted above the sinus level. They suspect that an alteration in cerebral haemodynamics must be concerned in the hypertension. In this connection it is of interest that Hawthorne and Greene (1950) found that bilateral frontal lobectomy or leucotomy in dogs did not abolish hypertension induced previously by Wakerlin's carotid sinus clamps.

McCubbin, Green and Page (1956) have made a study of electroneurograms of the carotid sinus in cellophane perinephritis hypertension in dogs They found that the baroceptor discharge commenced at a higher level in hypertensive animals and concluded that the baroceptors appear to be reset at a higher pressure level.

It is of interest that Heymans and Bouckaert (1938) and Hermann, Jourdan and Delrieu (1939) consider that vasoconstrictor ... are present in the bl...

by sec

sympat ... as 933F, (Govaerts and Verniory, 1952) rather favours the notion that such substances are likely to be sympathomimetic amines Another suggestion is that vasoconstrictor im-

ponding observations have been made in man to which reference is made elsewhere.

Sachs, Brendler and Fulton (1949) found that stimulation of the orbital gyri in the cat, dog and monkey gave rise to alterations in the blood pressure. The direction of blood pressure change depended to an important extent on the wave form of the electrical stimulation. Walter and Pijoan (1937) reported a number of large blood pressure rises in dogs which followed 3 mm. transverse incisions, immediately posterior to the infundibulum and deep enough to puncture the 3rd ventricle. Many other writers have described blood pressure rises from stimulation of various parts of the brain, but for the most part the changes are temporary and small, and so far experiments of this kind do not appear to have evoked substantial responses even from the nervous mechanisms which, in other circumstances, are known to cause large rises of blood pressure.

*Hypertension from interference with the carotid sinus and aortic nerves.* — It was shown by Hering (1927) that section of the aortic nerves and denervation of the carotid sinus led to a rise in blood pressure in the rabbit; anc [illegible] in other animals, notably the dog. [illegible] sion have been reviewed [illegible] pressure increase is associated with cardiac acceleration and increase of cardiac output (Bing, 1944). The blood pressure is exceedingly labile (Thomas, 1944). In dogs it commonly rises high when they are visited by the experimenter, and may fall away as they quieten down. The blood pressure is much decreased, sometimes even to normal, by anaesthesia and during sleep (Grimson, Kernodle and Hill, 1944; Page and McCubbin, 1951) The casual blood pressures may rise to great heights; Thomas (1944) reported pressures as high as 425 systolic and 222 diastolic in dogs with neurogenic hypertension of five years' duration. All observers are agreed that animals withstand this form of hypertension much better than experimental renal hypertension. The histological changes, when they occur, are milder and increases of heart size are less pronounced. One possible reason for this, not necessarily the only one, is the intermittent character of the blood pressure increase. Recently Dammin et al. (1956) have reported arteriolosclerotic lesions in 3 dogs with moderator nerve section and observed for 6, 7 and 7 years. The lesions appeared between 2 and 3½ years after hypertension was induced.

It seems to have been demonstrated that neurogenic hypertension as ordinarily produced by division of buffer nerves is labile and falls when the animal is at rest and unstimulated or under adequate sedation. Grimson (1949), however, expressed the view that neurogenic hypertension only fell towards normal levels at rest or under sedation when the denervation was inadequate. He considered that even with

increase persisted for at least several months after the audiogenic stimulation ended, and at that time there was no histological evidence of renal damage. In the course of a year the hypertension had subsided in almost all these rats.

In other experiments we exposed rats to the signal noise of a comparatively quiet buzzer following which the cage was electrified, causing a mild to moderate skin stimulation. This also led within a few weeks to a rise of blood pressure though of smaller degree. This blood [illegible]

hypertension. This would appear to be experimental confirmation in the rat of the suggestion that certain blood pressure increases, if frequent or prolonged enough, may outlive the stimuli which caused them. The blood pressure increases following audiogenic and electrical stimulation often persist after bilateral nephrectomy, and in this resemble the hypertension induced in rabbits by renal ischaemia (Pickering [illegible] whether a [illegible] audiogeni [illegible] due to the nephrectomy What appears to be certain is that stimuli of a nervous type can give rise to blood pressure elevations which persist for at least some months after the cessation of the nervous stimulation and which are not abolished by light ether anaesthesia. The mechanism of their production is unknown. We cannot eliminate the possibility of humoral agents such as renin or sympathomimetic amines, or adrenal cortical hormones entering the circulation as the result of the nervous stimulation

[illegible] cat [illegible] to [illegible] but the number of their animals was small. They inferred a rise in blood pressure.

*General remarks on inter-relationships between neurogenic and humoral hypertension* — The distinction between neurogenic and humoral mechanisms does not seem as precise to-day as it did years ago. Not only are [illegible] at presen[illegible] endings, [illegible] suggestion that such substances [illegible] perhaps other [illegible] tion o[illegible] worke[illegible] that following the stimulation of the central end of the vagus nerve in the neck noradrenaline is liberated into the blood stream from peripheral arteries.

Raab (1948) described the presence of a sympathomimetic amine in appreciable quantities in all parts of the human brain and in animal

pulses, leading to renal ischaemia, may be concerned in the sustained blood pressure elevation. Some say, and some deny, that renal denervation interferes with the maintenance of neurogenic hypertension.

*Hypertension from ligature of cerebral blood vessels.* — Blood pressure elevations have been reported to follow the ligature of the main blood vessels supplying the brain (Nowak and Walker, 1939; Fishback, Dutra and MacCamy, 1943 Rosenfeld, 1952); Taylor and Page (1951) found that cerebral ischaemia, severe enough to cause death in 41 per cent of the animals, induced arterial hypertension of 7 to 15 days' duration in only 24 per cent of those that lived. They found, however, that if in addition a tantalum wire was introduced into the floor of the fourth ventricle and heated by short-wave diathermy, then 64 per cent of the dogs developed hypertension, ordinarily of several months' duration.

*Hypertension from elevation of the intracranial tension.* — It is generally agreed that a rise in the intracranial tension regularly induces elevation of the blood pressure. Dixon and Heller (1932) produced rises of blood pressure by injections of kaolin into the cisterna magna of dogs. The authors regarded the hypertension as secondary to the increased intracranial pressure produced by obstruction of the subarachnoid spaces. There have been several confirmatory reports but a few investigators failed to obtain blood pressure increases. It was claimed by Braun and Samet (1935) that this method of inducing hypertension operated through the intermediation of the kidneys. Vasoconstrictor impulses involving the kidneys were thought to cause release of renin into the circulation. According to these authors, denervation of the kidneys prevents the rise of blood pressure from the intracisternal injection of kaolin.

*Hypertension from auditory and cutaneous electrical stimulation.* — Medoff and Bongiovanni (1945), Yeakel et al. (1948) and Farris et al. (1945) showed that rats subjected for long periods to intermittent audiogenic stimuli developed elevations of the blood pressure. The auditory stimulus was the release of an air blast for 5 minutes daily, 5 days a week and this was continued for a period of 400 to 900 days. The blood pressure rise only occurred as the rats increased in age. Restall and Smirk (1949) found, in agreement with Medoff and Bongiovanni, that the blood pressure elevations were not abolished by light ether anaesthesia. If, therefore, emotional disturbances were primarily responsible, it is of note that the hypertension persisted at a time when conscious cerebral processes were subdued by the anaesthetic.

The blood pressure elevation in our series was induced by a much more intense stimulation than an escape of air; namely, the noise of several electric motor horns in a confined space. Audiogenic fits were produced in several of the rats. We noted that the blood pressure

increase persisted for at least several months after the audiogenic stimulation ended, and at that time there was no histological evidence of renal damage. In the course of a year the hypertension had subsided in almost all these rats.

In other experiments we exposed rats to the signal noise of a comparatively quiet buzzer following which the cage was electrified, causing a mild to moderate skin stimulation. This also led within a few weeks to a rise of blood pressure though of smaller degree. This blood [illegible]

hypertension. This would appear to be experimental confirmation in the rat of the suggestion that certain blood pressure increases, if frequent or prolonged enough, may outlive the stimuli which caused them. The blood pressure increases following audiogenic and electrical stimulation often persist after bilateral nephrectomy, and in this resemble the hypertension induced in rabbits by renal ischaemia (Pickering, 1945). It must be pointed out that it has not been settled whether after bilateral nephrectomy the blood pressure rise induced by audiogenic stimulation is not merely replaced by a blood pressure rise due to the nephrectomy. What appears to be certain is that stimuli of a nervous type can give rise to blood pressure elevations which persist for at least some months after the cessation of the nervous stimulation and which are not abolished by light ether anaesthesia. The mechanism of their production is unknown. We cannot eliminate the possibility of humoral agents such as renin or sympathomimetic amines, or adrenal cortical hormones entering the circulation as the result of the nervous stimulation.

[illegible] ca [illegible] tc [illegible] the number of their animals was small. They inferred a rise in blood pressure.

[illegible] *hyp* [illegible] me[illegible] not seem as precise to-day as it did years ago. Not only are well-known substances such as noradrenaline, or a substance at present indistinguishable from it, liberated at sympathetic nerve endings, but there is at least a suggestion that such substances, and perhaps others too, may enter the blood stream as the result of stimulation of nervous tissue. In 1947 and 1948 Jiménez-Díaz and his co-workers (1954) reported that following the stimulation of the central end of the vagus nerve in the neck noradrenaline is liberated into the blood stream from peripheral arteries.

ap [illegible] human brain and in animal

brain. The substance has some properties in common with adrenaline and noradrenaline and others which differ. He has called it "encephalin". Binet and Burstein (1949a) consider that stimulation of the central end of the vagus gives rise to the release into the circulation of a pressor substance, the action of which is not reversed by 883F and is therefore not adrenaline. In a further paper (1949b) they think that the vasoconstrictor substances arise from the brain. A similar conclusion was reached by Taylor, Page and Corcoran (1951, 1955) who also believe that a substance "cerebrotonin" is released from the brain on stimulation of the central end of the cut vagus nerve and is probably not adrenaline or noradrenaline.

Reference should be made in this connection to a source of difficulty in interpreting the circulatory effects of experimental intervention with the nervous system. Hermann, Cier, Chatonnet and Vial (1947) and Chatonnet and Vial (1948) observed a progressive fall in rat blood pressure when the spinal cord is destroyed from below upwards. If, however, the animals are allowed to recover for a few days, then the blood pressure may rise once more almost to the original level. Similar results were obtained by Hermann, Morin and Vial (1936) in the dog.

In many animals following sympathectomy the blood pressure may fall, but later recovers itself. These results seem to be explained at least in part, by the experiments of Armin, Grant, Thompson and Tickner (1953) who showed that the heightened vascular reactivity of the denervated rabbit's ear was due to loss of the capacity to liberate acetylcholine at the periphery.

## Experimental Hypertension from Endocrine Substances Alone and in Conjunction with Salt

*Hypertension induced by salt administration* — Sapirstein, Brandt and Drury (1950) showed that in rats the administration of 1.5—2.5 per cent sodium chloride as drinking fluid leads to an elevation of the blood pressure. They think that "salt" hypertension is not abolished by bilateral adrenalectomy. Stamler and Katz (1951) have shown that salt hypertension can be produced also in chicks. Meneely, Tucker, Darby and Auerbach (1952) and Auerbach, Meneely, Tucker and Darby (1953) induced oedema and hypertension in rats by sodium chloride administration. We have also induced hypertension in rats in this way.

*Hypertension induced by desoxycorticosterone acetate and salt, by cortisone and other steroids.* — Ham (1940) and Mrazek, Novak and Reed (1942) obtained hypertension in rats by administration of [illegible] corticosterone. Similar observations were made by Grollman, [illegible] Knowlton et al. (1952) and by Selye [illegible] (1950) and Knowlton et al. (1952) both consider that salt is necessary for the hypertension which follows

the blood pressure. Cortisone [107] and Compound F [49] both raise the blood pressure but do not require the concurrent administration of salt. Aldosterone in amounts which were as effective as DOCA in salt retaining capacity, did not raise the blood pressure [60, 78] or cause pathological lesions. Aldosterone, however, had the capacity to maintain a normal blood pressure in Addison's disease [60]. Knowlton and her co-workers (1952) even find that the hypertension induced by cortisone in the adrenalectomized rat may be increased by salt restriction. According to Mach et al. (1954) and Gross et al. (1954) aldosterone differs from desoxycorticosterone in that it does not readily produce hypertension. There is good evidence that it is about twenty-five times as potent as desoxycorticosterone in causing sodium retention [78, 118].

Ledingham (1956) reports evidence that the adrenals in the absence of the kidneys cause withdrawal of sodium from the intracellular compartment in heart and skeletal muscle and that it is under these circumstances that renoprival hypertension arises. Orbison et al. (1956) also stress the importance of electrolytes. In bilaterally nephrectomized dogs the intraperitoneal injection of a variety of electrolyte solutions may induce hypertension and arterial necrosis. They think the anion may be important sometimes.

Hypertension in the cortisone-treated rats [107] was unassociated with histological evidence of renal damage, such as is normally observed in hypertensive animals receiving desoxycortic...

Knowlton et al. ...
the injection of rab...
sion if desoxycorti...
withdrawn the blood pressure declined.

Selye suggests that desoxycorticosterone acts on vessels only through the intermediation of the kidney. In the unilaterally nephrectomized rat desoxycorticosterone increases the rise of blood pressure from injections of angiotonin, whereas in bilaterally nephrecto...
desox...

of
H...
R...
resu...
on c...
enough do...
question a... ...sterone, methylstilboestrol, estradiol, testosterone, methylandrostenediol and 9 α-chlorohydrocortisone [154, 162].

U

*Effect of anterior pituitary extracts in inducing hypertension and renal damage.* — Hall and Selye (1945) showed that crude extracts of the anterior pituitary tissue of cattle lead, on injection, to enlargement of the adrenal cortex and, if administered to animals on a high sodium chloride intake, they cause enlargement of the kidneys, and lesions in the heart and kidneys similar to [illegible]

[illegible] et al. (1946) showed that lyophilised [illegible] hormone.

[illegible] the intermediation of the adrenal glands. Selye (1951b), working with electrophoretically pure somatotrophic hormone (STH), showed that this induces changes in the heart and kidney similar to those caused by toxic doses of mineralocorticoids such as DOCA. The possibilities are that STH leads to increase in the production of mineralocorticoids by the adrenal or that it sensitizes tissue to such substances. ACTH may also play a part though its effect is predominantly to produce secretion of glucocorticoids.

Guilleman and Fortier (1951) state that chlorpromazine prevents the functional and morphological changes associated with DOCA overdosage in sensitized animals. The animals were sensitized by unilateral nephrectomy and by administering 1 per cent sodium chloride in the drinking water. The rises in blood pressure were also prevented. In contrast histamine increased the effect of DOCA in sensitized rats.

## Effect of Thyroid Hormones on Experimental Hypertension

Selye (1950, 1951a) has reported the production of malignant hypertension when thyroxin (2 mg. daily) is administered to rats sensitized by unilateral nephrectomy and 1 per cent sodium chloride in place of drinking water. The hypertension may attain to 200 mm. Hg, and the simultaneous administration of ACTH, 6 mg. daily, or cortisone, 2.5 mg. daily, leads to a further increase in the nephrosclerosis. Braun-Menéndez (1954) has also noted that the blood pressure level in experimental renal hypertension is decreased by antithyroid drugs and increased by thyroid hormone.

## References


1 Abrams, M., and Sobin, S Latex rubber capsule for producing hypertension in rats by perinephritis Proc Soc exp Biol (N Y), 64 412, 1947.

2 Alpert, L. K., Alving, A. S, and Grimson, K S Effect of total sympathectomy on experimental renal hypertension in dogs Proc Soc. exp. Biol. (N.Y.), 37: 1, 1937.

3 ARMIN, J, GRANT, R. T, THOMPSON, R. H. S, and TICKNER, A An explanation for the heightened vascular reactivity of the denervated rabbit's ear J Physiol. (Lond), 121: 603, 1953.
4 AUERBACH, S H, MENEELY, G. R., TUCKER, R. C., and DARBY, W. J. Renal and vascular lesions induced in rats by a high salt diet. Fed Proc, 12: 384, 1953
5 BACKMANN, L Effet sur la pression artérielle de la néphrectomie et rôle probable des reins dans le système endocrine C. R. Soc. Biol. (Paris), 79: 406, 1916
6 BEST, C H, and HARTROFT, W. S Nutrition, renal lesions and hypertension. Fed Proc, 8: 610, 1949.
7 BINET, L., and BURSTEIN, M. Sur le pouvoir vasoconstricteur du sang artériel après excitation centripète du nerf vague chez le chien. C. R. Soc Biol. (Paris), 143: 1344, 1949a.
8 BINET, L., and BURSTEIN, M. Passage dans le sang d'une substance vasoconstrictrive d'origine céphalique après excitation centripète d'un nerf vague chez le chien. C. R. Soc. Biol. (Paris), 143. 1347, 1949b.
9 BING, R. J. The hemodynamics of neurogenic hypertension J. clin Invest, 23. 939, 1944
10 BING, R J, and ZUCKER, M. B Renal hypertension produced by amino acid J. exp. Med, 74: 235, 1941.
11 BLACKET, R. B, DEPOORTER, A., PICKERING, G W., SELLERS, A. L, and WILSON, G. M. Hypertension produced in the rabbit by long continued infusions of renin Clin Sci, 9: 223, 1950.
12 BLACKET, R. B, and SELLERS, A. L. The effect of removing the constriction of the renal artery in acute and chronic hypertension in the rabbit. Clin Sci, 10 177, 1951.
13 BRAUN, L, and SAMET, B Experimentelle Untersuchungen über Blutdruck und Niere IV. Wien klin Wschr, 48. 940, 1935.
14 BRAUN-MENÉNDEZ, E Hypertension and the relation between body weight and kidney weight Acta physiol [illegible]
15 [illegible]
16 [illegible]
17 [illegible]-MENENDEZ, E., FASCIOLO, J. C, LELOIR, L F., and MUÑOZ, J. M. La substancia hipertensora de la sangre del riñon isquemiado. Rev. Soc argent. Biol, 15. 420, 1939
18 BRAUN-MENÉNDEZ, E, FASCIOLO, J. C., LELOIR, L. F, and MUÑOZ, J. M. The substance causing renal hypertension J. Physiol. (Lond), 98: 283, 1940
19 [illegible] [illegible]IR, L F, and TAQUINI, A. C
20 [illegible] s. Springfield, Illinois, 1946.
[illegible] Hypertension after bilateral [illegible] Nature (Lond), 160: 905, 1947.
21 BURNS, R O, and WAKERLIN, G E Protection [illegible]
22 BYR[illegible]
23 BYR[illegible], and DODSON, L F. The causation of acute arterial necrosis in hypertensive disease. J. Path. Bact, 60: 357, 1948.
24 BYROM, F B, and DODSON, L. F The mechanism of the vicious circle in chronic hypertension. Clin Sci, 8, 1, 1949

25 CASH, J. R. A preliminary study of the blood-pressure following reduction of renal substance with a note on simultaneous changes in blood-chemistry and blood-volume. Bull. Johns Hopk. Hosp., 35: 168, 1924

26 CASH, J. R. Further studies of arterial hypertension Proc. Soc. exp. Biol (N.Y.), 23: 609, 1925—26.

27 CERQUA, S., and SAMAAN, A. Cure of experimental renal hypertension Clin. Sci, 4: 113, 1939.

28 CHATONNET, J, and VIAL, J. Evolution de la pression artérielle au cours de la destruction de la moelle chez le rat. C. R. Soc. Biol. (Paris), 142: 97, 1948.

29 CLEGHORN, R. A, FOWLER, J. L. A., GREENWOOD, W. F., and CLARKE, A. P. W. Pressor responses in healthy adrenalectomized dogs Amer. J. Physiol., 161: 21, 1950.

30 COLLINS, D. A. Hypertension from constriction of arteries of denervated kidneys Amer. J. Physiol., 116: 616, 1936.

31 COLLINS, D. A, and WOOD, E. H. Experimental renal hypertension and adrenalectomy. Amer. J. Physiol., 123: 224, 1938.

32 CORBIT, J. D. Effect of pregnancy upon experimental hypertension in rabbit. Amer. J med. Sci., 201: 876, 1941

32a CRANDALL, E., and WAKERLIN, G. E Pathogenesis of experimental hypertension in dogs produced by carotid sinus area constriction. Fed. Proc, 15: 42, 1956.

32b DAMMIN, G J., GOLDMAN, M. L, SCHROEDER, H A., and PAGE, M. G Arterial hypertension in dogs II. The effects of neurogenic hypertension with a study of periodic renal biopsies over a seven-year period. Lab. Invest., 5: 72, 1956

33 DANIEL, P M., PRICHARD, M. M L, and WARD-McQUAID, J. N Removal of the clip on the renal artery in rabbits with experimental chronic hypertension Quart. J. exp Physiol, 39: 101, 1954a

34 DANIEL, P M, PRICHARD, M. M L., and WARD-McQUAID, J. N Total nephrectomy in rabbits with chronic hypertension Clin. Sci, 13: 247, 1954b

35 DAVIS, L, TANTURI, C, and TARKINGTON, J. The effect of reduced blood flow to the liver in renal hypertension. Surg Gynec Obstet, 89: 360, 1949.

36 DICKER, E. Recherches expérimentales concernant le mécanisme de l'hypertension d'orgine rénale chez le chien. Arch int Méd exp, 13. 27, 1938

37 DILL, L. V, and ERICKSON, C C Effect of constriction of the renal [illegible] ...ts Arch [illegible]

38 DIX[illegible] ...rtension by increasing intracranial pressure. Arch exp Path Pharmak, 166: 265, 1932.

39 DOCK, W. Vasoconstriction in renal hypertension abolished by pithing. Amer. J. Physiol, 130 1, 1940

40 FARRIS, E. J., YEAKEL, E. H., and MEDOFF, H S Development of hypertension in emotional gray Norway rats after air blasting Amer. J Physiol, 144· 331, 1945.

41 FASCIOLO, J. C., HOUSSAY, B. A, and TAQUINI, A C The blood pressure raising secretion of the ischaemic kidney J Physiol. (Lond), 94· 281, 1938.

42 FISHBACK, H. R., DUTRA, F. E., and MACCAMY, E T. The production of chronic hypertension in dogs by progressive ligation of arteries supplying the head J Lab. clin. Med, 28: 1187, 1943.

43 FLEMING, H. A. Unpublished observations Cited by Smirk, F. H., Brit. med J, 1: 791, 1949
44 FLEMING, H. A. Factors involved in the production of acute arterial lesions in rabbits with experimental renal hypertension. J. Path. Bact, 65: 441, 1953.
45 FLOYER, M. A. The effect of nephrectomy and adrenalectomy upon the blood pressure in hypertensive and normotensive rats Clin. Sci, 10: 405, 1951.
46 FLOYER, M A. Further studies on the mechanism of experimental hypertension in the rat. Clin. Sci., 14: 163, 1955
47 FREEMAN, N. E, and PAGE, I. H. Hypertension produced by constriction of the renal artery in sympathectomised dogs. Amer. Heart J., 14: 405, 1937
48 FRIEDEN, J, STAMLER, J., HWANG, W., KURAMOTO, K, and KATZ, L. N. Depressor effect of chronic salt depletion in renal hypertensive dogs. J. Lab clin Med, 38: 810, 1951.
49 FRIEDMAN, S M., FRIEDMAN, C. L, and NAKASHIMA, M. Further observations on the hypertensive properties of compound F acetate in the rat. Endocrinology, 53: 633, 1953.
50 GAUNT, R, RENZI, A. A, and CHART, J. J. Aldosterone — A review. J. clin Endocr, 15: 621, 1955.
51 GLENN, F, CHILD, C G, and HEUER, G J. Hypertension experimentally produced by constricting the artery of a single transplanted kidney. Ann. Surg, 107: 618, 1938.
52 GOLDBLATT, H Studies on experimental hypertension. III. The production of persistent hypertension in monkeys (macaque) by renal ischemia. J exp Med, 65. 671, 1937.
53 GOLDBLATT, H Studies on experimental hypertension; production of the malignant phase of hypertension. J. exp. Med., 67: 809, 1938
54 GOLDBLATT, H The renal origin of hypertension. Physiol. Rev., 27: 120, 1947
55 GOLDBLATT, H, GROSS, J., and HANZAL, R. F. Studies on experimental hypertension: The effect of resection of splanchnic nerves on experimental renal hypertension J exp Med, 65: 233, 1937.
56 GOLDBLATT, H, HAAS, E., and LAMFROM, H. Antirenin in man and animals. Trans Ass Amer. Phys., 64: 122, 1951
57 GOLDBLATT, H., KAHN, J. R, and HANZAL, R. F Studies on experimental hypertension. The effect on blood pressure of constriction of the abdominal aorta above and below the site of origin of both main renal arteries J exp. Med, 69. 649, 1939
58 GOLDBLATT, H, KAHN, J. R., and LEWIS, H A. The production of persistent hypertension in sheep and goats (Studies on experimental hypertension. XIX). Amer Heart J, 26: 567, 1943.
59 GOLDBLATT, H, LYNCH, J., HANZAL, R F., and SUMMERVILLE, W. W. Studies on experimental hypertension I. The production of persistent elevation of systolic blood pressure by means of renal ischemia J. exp. Med 59: 347, 1934.
60 GOLDBLATT, H, and WARTMAN, W. B Studies on experimental hypertension. VI The effect of section of anterior spinal nerve roots on experimental hypertension due to renal ischemia. J. exp Med, 66: 527, 1937
61 GOLLAN, F., RICHARDSON, E., and GOLDBLATT, H. Hypertensin in the systemic blood of animals with experimental renal hypertension. J. exp Med, 88: 389, 1948

62 Goormaghtigh, N., and Handovsky, H. Effect of vitamin $D_2$ (calciferol) on the dog. Arch. Path. (Chicago), **26**: 1144, 1938

63 Govaerts, P. *Recherches sur l'action hypertensive du rein.* Bull. Acad Méd. Belg., **4**: 357, 1939.

64 Govaerts, P., and Verniory, A. Effet du 933F sur l'action vasoconstrictive du sang cave dans l'hypertension rénale expérimentale chez le chien. Bull. Acad. Méd. Belg., **17**: 355, 1952.

65 Grimson, K. S. Role of sympathetic nervous system in hypertension as revealed by the action of sympatholytic and depressor drugs. Factors Regulating Blood Pressure, Transactions of the Third Macy Conference, Josiah Macy Jr. Foundation, New York, 1949.

66 Grimson, K. S., Kernodle, C. E., and Hill, H. C. Hypertension — The effect of activity, rest, natural sleep, sodium amytal, pentothal sodium, chloralose and ether on experimental neurogenic hypertension and of rest and sodium amytal and anesthesia on hypertensive patients J Amer med Ass, **126**: 218, 1944.

67 Grollman, A. A simplified procedure for inducing chronic renal hypertension in the mammal. Proc Soc. exp. Biol. (N.Y.), **57**: 102, 1944a

68 Grollman, A. Experimental chronic hypertension in the rabbit. Amer J. Physiol., **142**: 666, 1944b.

69 Grollman, A. Experimental hypertension in the dog. Amer J. Physiol, **147**: 647, 1946

70 Grollman, A. Effect of increasing the extracellular fluid volume on the arterial blood pressure of the normal, hypertensive and nephrectomised dog Amer J. Physiol, **173**: 364, 1953

71 Grollman, A., and Halpert, B. Renal lesions in chronic hypertension induced by unilateral nephrectomy in the rat. Proc. Soc exp Biol. (N.Y.), **71**: 394, 1949.

72 Gro[illegible] restriction on [illegible] (N Y)

73 Grollman, A, Harrison, T. R, and Williams, J R, Jr Effect of various sterol derivatives on the blood pressure of the rat. J Pharmacol, **69**: 149, 1940.

74 Grollman, A, Muirhead, E. E., and Vanatta, J. Rôle of kidney in pathogenesis of hypertension as determined by study of effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog Amer. J Physiol, **157**: 21, 1949

75 Grollman, A, and Rule, C. Experimentally induced hypertension in parabiotic rats Amer J Physiol, **138**: 587, 1943

76 Grollman, A, and Shapiro, A. P The volume of the extracellular fluid in experimental and human hypertension J clin Invest, **32** 312, 1953

77 Grollman, A., Vanatta, J, and Muirhead, E E Rôle of the kidney in the pathogenesis of experimental hypertension. Amer J Med, **7** 251, 1949.

78 [illegible] Untersuchungen [illegible]

79 [illegible] and hyalinosis by a drug acting on membrane [illegible] docrinology, **48** 617, 1951

80 Hall, C. E, Dontigny, P., Beland, E, and Selye, H The rôle of the adrenals in the production of nephrosclerosis by anterior pituitary preparations. Endocrinology, **38**: 296, 1946

81 HALL, C E, and SELYE, H Prevention of the nephrosclerosis usually induced by anterior pituitary extract. Rev. canad Biol, 4: 197, 1945.
82 HAM, A. W. Coronary and aortic sclerosis, periarteritis nodosa, chronic nephritis and hypertension as sequelae to a single experimentally produced widespread calcium precipitation in the rat. Arch. Path (Chicago), 29: 731, 1940
83 HANTSCHMANN, L Blutdrucksteigerung durch Kochsalzgaben beim Hunde nach experimenteller Ausschaltung von Nierengewebe Z ges exp Med, 79. 1, 1931
84 HARTMAN, F W, BOLLIGER, A, and DOUB, H P Experimental nephritis produced by irradiation Amer J med. Sci, 172: 487, 1926
85 HARTMAN, F. W, BOLLIGER, A, and DOUB, H. P. The cardiovascular response in experimental nephritis. J. Amer. med Ass, 89: 1936, 1927.
86 HARTROFT, W. S Pathogenesis of renal lesions in weaning and young adult rats fed choline-deficient diets Brit. J. exp Path, 29 483, 1948
87 HARTWICH, A Der Blutdruck bei experimenteller Urämie und partieller Nierenausscheidung Z. ges. exp Med, 69. 462, 1930
87a HAWTHORNE, E. W, and GREENE, C. S. Absence of an antihypertensive effect of bilateral frontal lobectomy or leucotomy in dogs hypertensive from bilateral carotid sinus constriction Fed Proc, 15. 89, 1956
88 HERRING, H E. Die reflektorische Selbststeuerung des Blutdruckes vermittelst der Blutdruckzugler. Z KreislForsch., 19: 410, 1927
89 HERMANN, H, CIER, J F., CHATONNET, J, and VIAL, J. Les conditions de la "Vie sans Moelle" chez le rat C. R. Soc Biol. (Paris), 141: 934, 1947
90 HERMANN, H, JOURDAN, F, and DELRIEU, A Sur la présence de substances vaso-constrictives dans le sang des chiens hypertendus par la section de leurs nerfs frénateurs Arch Mal Coeur, 32· 545, 1939
91 HERMANN, H, MORIN, G, and VIAL, J Les régulations périphériques chez le chien sans moelle· II. Evolution de la pression artérielle après la destruction de la moelle dorso-lombo-sacrée. Arch int Physiol, 44: 125, 1936—37
92 HEYMANS, C The pressoreceptive mechanisms for the regulation of heart rate, vasomotor tone, blood pressure and blood supply. New Engl J Med, 219. 147, 1938a
93 HEYMANS, C Experimental arterial hypertension New Engl. J. Med, 219. 154, 1938b.
94 HEYMANS, C, and BOUCKAERT, J J Hypertension artérielle expérimentale et sympathectomie. C R Soc Biol. (Paris), 120: 82, 1935
95 [illegible]
96 [illegible]
97 HEYMANS, C, BOUCKAERT, J J, ELAUT, L, BAYLESS, F., and SAMAAN, A. Hypertension artérielle chronique par ischémie rénale chez le chien [illegible]
98 HILL [illegible]
98a HOF [illegible]
98b HOUCK, C R Renoprival hypertension in totally sympathectomized dogs. Fed Proc., 15· 96, 1956

62 GOORMAGHTIGH, N., and HANDOVSKY, H. Effect of vitamin $D_2$ (calciferol) on the dog. *Arch. Path. (Chicago), 26: 1144, 1938.*

63 GOVAERTS, P. Recherches sur l'action hypertensive du rein. Bull Acad Méd. Belg., 4: 357, 1939.

64 GOVAERTS, P., and VERNIORY, A. Effet du 933F sur l'action vasoconstrictive du sang cave dans l'hypertension rénale expérimentale chez le chien Bull. Acad. Méd. Belg., 17: 355, 1952.

65 GRIMSON, K. S. Role of sympathetic nervous system in hypertension as *revealed by the action of sympatholytic and depressor drugs* Factors Regulating Blood Pressure, Transactions of the Third Macy Conference, Josiah Macy Jr. Foundation, New York, 1949

66 GRIMSON, K. S., KERNODLE, C. E., and HILL, H. C. Hypertension — The effect of activity, rest, natural sleep, sodium amytal, pentothal sodium, chloralose and ether on experimental neurogenic hypertension and of rest and sodium amytal and anesthesia on hypertensive *patients J Amer med Ass., 126: 218, 1944*

67 GROLLMAN, A. A simplified procedure for inducing chronic renal hypertension in the mammal. Proc. Soc. exp. Biol. (N Y.), 57: 102, 1944a.

68 GROLLMAN, A. Experimental chronic hypertension in the rabbit. Amer. J Physiol., 142: 666, 1944b

69 GROLLMAN, A Experimental hypertension in the dog Amer J. Physiol, 147. 647, 1946

70 GROLLMAN, A. *Effect of increasing the extracellular fluid* volume on the arterial blood pressure of the normal, hypertensive and nephrectomised dog. Amer J. Physiol, 173: 364, 1953.

71 GROLLMAN, A., and HALPERT, B. Renal lesions in chronic hypertension induced by unilateral nephrectomy in the rat. Proc. Soc exp Biol. (N Y.), 71: 394, 1949.

72 GROLLMAN, A, and HARRISON, T. R. Effect of rigid sodium restriction on pressure and survival of hypertensive rats Proc Soc exp Biol (N.Y) 60: 52, 1945.

73 GROLLMAN, A, HARRISON, T R, and WILLIAMS, J. R, Jr Effect of various sterol derivatives on the blood pressure of the rat. J Pharmacol., 69: 149, 1940

74 GROLLMAN, A, MUIRHEAD, E. E., and VANATTA, J. Rôle of kidney in pathogenesis of hypertension as determined by study of effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog. Amer J Physiol., 157: 21, 1949

75 GROLLMAN, A, and RULE, C. Experimentally induced hypertension in parabiotic rats Amer J. Physiol, 138· 587, 1943

76 GROLLMAN, A, and SHAPIRO, A. P The volume of the extracellular fluid in experimental and human hypertension J. clin Invest, 32 312, 1953

77 GROLLMAN, A, VANATTA, J, and MUIRHEAD, E E Rôle of the kidney in *the pathogenesis of experimental hypertension* Amer J. Med., 7 251 1949

78 GROS [illegible]

79 GUILLEMAN, R, and FORTIER, C Inhibition of DCA induced hypertension and hyalinosis by a drug acting on membrane permeability Endocrinology, 48: 617, 1951

80 HALL, C. E., DONTIGNY, P., BELAND, E, and SELYE, H The rôle of the adrenals in the production of nephrosclerosis by anterior pituitary preparations Endocrinology, 38. 296, 1946

118 MACH, R. S., FABRE, J., DUCKERT, A., BORTH, R., and DUCOMMUN, P. Clinical and metabolic action of aldosterone (electrocortin). Schweiz. med. Wschr., 84: 407, 1954.

119 MEDOFF, H. S., and BONGIOVANNI, A. M. Blood pressure in rats subjected to audiogenic stimulation. Amer. J. Physiol., 143: 300, 1945

120 MENEELY, G. R., TUCKER, R. G., DARBY, W. J., and AUERBACH, S. H. Hypertension, edema and renal failure produced in the rat by high salt diet. Amer. J. Physiol., 171: 750, 1952.

121 [illegible]

122 [illegible]

123 [illegible] 12: 397, 1953.

124 MUIRHEAD, E. E., GROLLMAN, A., and VANATTA, J. Hypertensive cardiovascular disease (malignant hypertension). Change in canine tissues induced by various manipulations of the kidney with special reference to vascular and myocardial lesions. Arch. Path. (Chicago), 50: 137, 1950

125 MUIRHEAD, E. E., JONES, F., and GRAHAM, P. Hypertension following bilateral nephrectomy of the dog: The influence of dietary protein on its pathogenesis with emphasis on its development in the absence of "extracellular fluid" expansion. Circulation Research, 1: 439, 1953

126 MUI[illegible]

127 MUIRHEAD, E. E., VA[illegible] vascular disease [illegible] ally nephrectomi[illegible]

128 NICKERSON, M., BULLOCK, F., and NOMAGUCHI, G. M. Effect of dibenamine on renal hypertension in rats. Proc. Soc. exp. Biol. (N.Y.), 68: 425, 1948

129 NOWAK, S. J. G., and WALKER, I. J. Experimental studies concerning the nature of hypertension — Their bearing on surgical treatment. New Engl. J. Med., 220: 269, 1939

130 OGDEN, E. The extra-renal sequel to experimental renal hypertension. Bull. N.Y. Acad. Med., 23: 643, 1947.

131 OGDEN, E. Factors Regulating Blood Pressure. Transactions of the Third Macy Conference, Josiah Macy Jr. Foundation, New York, p. 103, 1949

132 OPPENHEIMER, B. S., ROSENAK, S. S., and OPPENHEIMER, G. D. blood pressures of chronic hypertensive dogs surviving bilateral nephrectomy. J. Mt. Sinai Hosp., 19: 266, 1952

133 ORBISON, J. L., CHRISTIAN, C. L., and PETERS, E. Studies on experimental hypertension and cardiovascular disease. I. A method for the rapid production of malignant hypertension in bilaterally nephrectomised dogs. Arch. Path. (Chicago), 54: 185, 1952

133a ORBISON, J. L., PETERS, E., and CHRISTIAN, C. L. Studies on experimental hypertension and cardiovascular disease. II. The effects of fluid and electrolyte on bilaterally nephrectomized dogs. Arch. Path., 61: 450, 1956

99 Houssay, B A., and Fasciolo, J. C. Sécrétion hypertensive du rein ischémié. C. R. Soc. Biol. (Paris), 127: 147, 1938.
100 Houck, C. R. Effect of hydration and dehydration on hypertension in the chronic bilaterally nephrectomised dog. Amer. J. Physiol, 176: 183, 1954.
101 Jiménez-Diaz, C., de la Barreda, P., and de Molina, A. F. Internal secretion of the arterial wall in blood pressure regulation. Ciba Foundation Symposium on Hypertension. J. & A. Churchill Ltd., London, p. 58, 1954.
102 Kahn, J. R., Skeggs, L. T., and Shumway, N. P. Isolation of hypertensin from circulating blood of dogs by dialysis in an artificial kidney Circulation (N.Y.), 2: 363, 1950.
103 Katz, L N., Friedman, M., Rodbard, S., and Weinstein, W. Observations on the genesis of renal hypertension Amer. Heart J., 17: 334, 1939.
104 Katz, L. N., Mendlowitz, M, and Friedman, M. A study of the factors concerned in renal hypertension. Proc Soc. exp. Biol. (N.Y.), 37: 722, 1938.
105 Katz, L. N, Rodbard, S., and Meyer, J. Blood pressure responses of dogs to vitamin A and Vitamin $D_2$ Amer. J. Physiol., 140: 226, 1943.
106 Knowlton, A. I., Loeb, E. N., Seegal, B. C, and Stoerk, H. C. Desoxycorticosterone acetate: Studies on the reversability of its effects on blood pressure and renal damage in rats. Endocrinology, 45: 435, 1949.
107 Knowlton, A I, Loeb, E N, Stoerk, H C, White, J. P, and Heffernan, J. F. Induction of arterial hypertension in normal and adrenalectomised rats given cortisone acetate. J exp Med., 96: 187, 1952
108 Kohlstaedt, K. G., Helmer, O. M, and Page, I. H. Activation of renin by blood colloids. Proc. Soc. exp. Biol. (N Y.), 39. 214, 1938
109 Kohlstaedt, K G., and Page, I. H. Liberation of renin by perfusion of kidneys following reduction of pulse pressure J. exp Med., 72. 201, 1940.
110 Kohlstaedt, K G., Page, I. H, and Helmer, O M. The activation of renin by blood. Amer. Heart J., 19. 92, 1940
111 Kolff, W. J, and Page, I. H. Renoprival hypertension and antirenin. Amer. J Physiol, 181. 575, 1955.
112 Ledingham, J M. The nature of the hypertension occurring in the nephrectomized parabiotic rat Clin Sci, 10· 423, 1951.
112a Ledingham, J M Electrolyte disturbances in experimental hypertension Acta. med. scand., suppl. 312· 251, 1956
113 Leloir, L. F, Muñoz, J. M., Braun-Menéndez, E., and Fasciolo, J. C. Sécrétion de rénine et formation d'hypertensine. C R Soc. Biol (Paris), 134: 487, 1940
114 Leonards, J. R, and Heisler, C R Artificial kidney. Maintenance of life in bilaterally nephrectomised dogs and its relation to malignant hypertension Amer J. Physiol, 167: 553, 1951
115 Leonards, J. R., and Heisler, C R Blood pressure of bilaterally nephrectomised dogs Fed Proc, 11. 247, 1952
115a McCubbin, J. W, Green, J. H, and Page, I H Baroceptor function in chronic renal hypertension. Circulation Res, 4: 205, 1956
116 McQueen, E. G. Personal communication
116a McQueen, E. G. Vascular reactivity in experimental renal and renoprival hypertension. Clin. Sci, in press
117 McQueen, E. G., and Veale, A. M O Vascular reactivity in renoprival hypertension Proc Univ Otago med. Sch, 33: 34, 1955.

118 MACH, R. S., FABRE, J., DUCKERT, A., BORTH, R., and DUCOMMUN, P. Clinical and metabolic action of aldosterone (electrocortin). Schweiz. med Wschr., 84: 407, 1954.

119 [illegible]

120 [illegible] Hypertension, edema and renal failure produced in the rat by high salt diet. Amer. J Physiol., 171: 750, 1952.

121 MRAZEK, R. G., JENSIK, R. J., and REED, C. I. The influence of an activated sterol on blood pressure in dogs. Amer. J. Path., 20: 857, 1944

122 MRAZEK, R., NOWAK, C. G., and REED, C. I. Further study of the influence of activated sterols on blood pressure. Fed. Proc., 1: 61, 1942

123 MUIR[illegible] 12. 391, 1953.

124 MUIRHEAD, E. E., GROLLMAN, A., and VANATTA, J. Hypertensive cardiovascular disease (malignant hypertension). Change in canine tissues induced by various manipulations of the kidney with special reference to vascular and myocardial lesions. Arch. Path. (Chicago), 50: 137, 1950

125 MUIRHEAD, E. E., JONES, F., and GRAHAM, P. Hypertension following bilateral nephrectomy of the dog: The influence of dietary protein on its pathogenesis with emphasis on its development in the absence of "extracellular fluid" expansion. Circulation Research, 1: 439, 1953

126 MUIRHEAD, E. E., STIRMAN, J. A., JONES, F., LESCH, W., BURNS, M., and FOGELMAN, M. J Cardiovascular lesions following bilateral nephrectomy of dog — Rôle of hypertension and other factors on pathogenesis Arch intern Med., 91: 250, 1953

127 MUIRHEAD, E. E., VANATTA, J., and GROLLMAN, A. Hypertensive cardiovascular disease An experimental study of tissue changes in bilaterally nephrectomised dogs Arch Path (Chicago), 48: 234, 1949.

128 NICKERSON, M., BULLOCK, F., and NOMAGUCHI, G M. Effect of dibenamine on renal hypertension in rats Proc Soc. exp. Biol. (N.Y.), 68: 425, 1948.

129 NOWAK, S J G., and WALKER, I J Experimental studies concerning the nature of hypertension — Their bearing on surgical treatment. New Engl J Med., 220 269, 1939

130 OGDEN, E The extra-renal sequel to experimental renal hypertension. Bull N Y Acad. Med., 23. 643, 1947

131 OGDEN, E Factors Regulating Blood Pressure. Transactions of the Third Macy Conference, Josiah Macy Jr. Foundation, New York, p. 103, 1949

132 OPPENHEIMER, B S., ROSENAK, S S., and OPPENHEIMER, G. D. blood pressures of chronic hypertensive dogs surviving bilateral nephrectomy J Mt Sinai Hosp., 19: 266, 1952

133 ORBISON, J L., CHRISTIAN, C. L., and PETERS, E. Studies on experimental hypertension and cardiovascular disease. I A method for the rapid production of malignant hypertension in bilaterally nephrectomised dogs Arch Path (Chicago), 54 185, 1952

133a ORBISON, J L., PETERS, E., and CHRISTIAN, C L Studies on experimental hypertension and cardiovascular disease. II. The effects of fluid and electrolyte on bilaterally nephrectomized dogs Arch. Path., 61: 456, 1956

134 PAGE, I. H. The relationship of the extrinsic renal nerves to the origin of experimental hypertension. Amer. J. Physiol., 112. 166, 1935

135 PAGE, I. H. The effect of bilateral adrenalectomy on arterial blood pressure of dogs with experimental hypertension. Amer. J. Physiol, 122. 352, 1938.

136 PAGE, I H. The production of persistent arterial hypertension by cellophane perinephritis. J. Amer. med. Ass., 113: 2046, 1939.

137 PAGE, I H. Influence of the liver on vascular reactivity. Amer. J. Physiol, 160 421, 1950

138 PAGE, I. H., and HELMER, O. M A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. J. exp. Med., 71: 29, 1940

139 PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., FOUTS, P. J, and KEMPF, G. F. Reduction of arterial blood pressure of hypertensive patients and animals with extracts of kidneys J. exp. Med, 73 7, 1941

140 PAGE, I H, and MCCUBBIN, J. The pattern of vascular reactivity in experimental hypertension of varied origin Circulation (N Y.), 4' 70, 1951

141 PAGE, I. H., and SWEET, J. E. Effect of hypophysectomy on arterial blood pressure of dogs with experimental hypertension Amer J. Physiol, 120: 238, 1937.

142 PHILLIPSBORN, [illegible] diets on ex[illegible]

143 PICKERING, G. [illegible] following [illegible] 1945

144 PICKERING, G W, and PRINZMETAL, M Some observations on renin, a pressor substance contained in normal kidney, together with a method for its biological assay. Clin Sci, 3. 211, 1938

145 PICKERING, G W, PRINZMETAL, M, and KELSALL, A R Assay of renin in rabbits with experimental renal hypertension. Clin Sci, 4: 401, 1942.

146 RAAB, W Specific sympathomimetic substance in the brain Amer J Physiol, 152 324, 1948.

147 RAU, G. C. Experimental hypertension produced by a plastic capsule applied to the kidney Science, 111 229, 1950

148 RESTALL, P A. Unpublished observation Cited by Smirk, F H. Brit med J, 1: 791, 1949.

149 RESTALL, P A, and SMIRK, F H Unpublished observations Cited by Smirk, F H, Brit med J, 1: 791, 1949

150 RODBARD, S, and KATZ, L N The rôle of renal metabolism in hypertension and uremia., J exp Med., 73 357, 1941

151 ROSENFELD, S Production of persistent hypertension induced in the rabbit by occlusion of arteries supplying the brain Amer J Physiol, 169: 733, 1952

152 RYTAND, D A. The renal factor in arterial hypertension with coarctation of the aorta J clin. Invest, 17 391, 1938

153 SACHS, E., Jr., BRENDLER, S J, and FULTON, J. F. The orbital gyri Brain, 72: 227, 1949

154 SALDAGO, E, and SELYE, H. The rôle of the adrenals in the production of cardiovascular and renal changes by methylandrostenediol Arch. int. Physiol, 62· 352, 1954

155 SAPIRSTEIN, L. A, BRANDT, W. L, and DRURY, D. R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water Proc. Soc exp Biol (N.Y.), 73: 82, 1950.

156 SCHROEDER, H A., and ADAMS, M. H. The effect of tyrosinase on experimental hypertension J. exp Med, 73: 531, 1941.
157 SCHUNK, J., and CORNELIUS, H V. Morphologischer Organerkrankungen auf emotionaler Grundlage im Tierexperiment. Z. ges. exp Med, 120: 101, 1952
158 SECKER, J The rôle of the adrenal cortex in the maintenance of the sciatic pressor reflex. J. Physiol (Lond), 109: 49, 1949.
159 SELYE, H. Production of hypertension and hyalinosis by desoxycortisone. Brit med. J, 1: 203, 1950
160 SELYE, H. Production d'une hypertension et d'une néphrosclérose maligne par la thyroxine chez le rat. Rev. canad. Biol, 9: 475, 1951a
161 SELYE, H Rôle of somatotrophic hormone in the production of malignant nephrosclerosis, periarteritis nodosa, and hypertensive disease. Brit med. J, 1: 263, 1951b
162 SELYE, H On the toxicity of 9α-fluorohydrocortisone and 9α-chlorohydrocortisone. J. clin. Endocr., 15: 384, 1955.
163 SHIPLEY, R. E, HELMER, O M., and KOHLSTAEDT, K. G. The presence in blood of a principle which elicits a sustained pressor response in [illegible]
164 [illegible]
165 [illegible] vasoactive factors, VEM and VDM Factors Regulating Blood Pressure Transactions of the Fourth Macy Conference, Josiah Macy Jr Foundation, New York, p. 185, 1950
166 SHORR, E, ZWEIFACH, B W, FURCHGOTT, R. F, and BAEZ, S Hepatorenal factors in circulatory homeostasis. XII. Alterations in renal vaso-excitor mechanisms during experimental hypertension. Fed Proc, 6. 200, 1947
167 STAMLER, J, and KATZ, L N The effect of "salt" hypertension on atherosclerosis in chicks fed mash without a cholesterol supplement Circulation (N Y), 3 859, 1951
168 STAMLER, J, RODBARD, S, KATZ, L N, and FISHMAN, A P. Cardiodynamic and renal changes in spontaneous and nephrogenic hypertensive dogs in response to tissue injury J. Lab. clin. Med, 34: 1753, 1949
169 TAGGART, J, and DRURY, D R The action of renin on rabbits with renal hypertension J exp. Med, 71 857, 1940
170 TAYLOR, R. D, and PAGE, I H Production of prolonged arterial hypertension in dogs by chronic stimulation of the nervous system — Exploration of the mechanism of hypertension accompanying increased intracranial pressure Circulation (N.Y.), 3: 551, 1951.
170a TAYLOR, R D, and PAGE, I H Vasopressor substance (cerebrotonin) of central origin Amer J Physiol, 183· 12, 1955.
171 TAYLOR, R D, PAGE, I. H, and CORCORAN, A. C A hormonal neurogenic vasopressor mechanism. Arch intern Med., 88: 1, 1951.
172 THOMAS, C B Experimental hypertension from section of moderator nerves The relationship of the acute pressor response to the development and course of chronic hypertension J. clin. Invest, 23: 927, 1944
173 TIGERSTEDT, R, and BERGMAN, P G Niere und Kreislauf. Skand Arch. Physiol, 8· 223, 1898
174 TOBIAN, L., Jr. Hypertension following bilateral nephrectomy. J. clin Invest, 29. 849, 1950.

134 PAGE, I. H. The relationship of the extrinsic renal nerves to the origin of experimental hypertension. Amer. J. Physiol., 112 166, 1935

135 PAGE, I. H. *The effect of bilateral adrenalectomy* on arterial blood pressure of dogs with experimental hypertension. Amer. J. Physiol, 122: 352, 1938.

136 PAGE, I. H. The production of persistent arterial hypertension by cellophane perinephritis. J. Amer. med. Ass., 113: 2046, 1939.

137 PAGE, I H. Influence of the liver on vascular reactivity. Amer. J. Physiol, 160· 421, 1950.

138 PAGE, I. H., and HELMER, O. M. A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. J. exp. Med., 71: 29, 1940.

139 PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., FOUTS, P. J., and KEMPF, G. F. *Reduction of arterial blood pressure of hypertensive* patients and animals with extracts of kidneys J. exp Med, 73. 7, 1941

140 PAGE, I. H., and MCCUBBIN, J *The pattern of vascular reactivity in* experimental hypertension of varied origin Circulation (N Y.), 4: 70, 1951.

141 PAGE, I. H., and SWEET, J. E *Effect of hypophysectomy on arterial blood* pressure of dogs with experimental hypertension. Amer. J. Physiol, 120: 238, 1937.

142 PHILLIPSBORN, H, KATZ, L. N., and RODBARD, S. Effect of high protein [illegible] 1941

143 PICK [illegible] 1945

144 PICKERING, G W, and PRINZMETAL, M Some observations on renin, a pressor substance contained in normal kidney, together with a method for its biological assay Clin Sci, 3 211, 1938.

145 PICK[illegible] Assay of renin in [illegible]

146 RAA[illegible] *Physiol, 152. 324, 1948*

147 RAU, G. C. Experimental hypertension produced by a plastic capsule applied to the kidney Science, 111 229, 1950

148 RESTALL, P A *Unpublished observation* Cited by Smirk, F H. Brit med J, 1. 791, 1949

149 RESTALL, P A, and SMIRK, F. H Unpublished observations Cited by Smirk, F H., Brit med. J, 1 791, 1949

150 RODBARD, S, and KATZ, L N The rôle of renal metabolism in hypertension and uremia, J exp. Med, 73· 357, 1941

151 ROSENFELD, S Production of persistent hypertension induced in the rabbit by occlusion of arteries supplying the brain Amer. J Physiol, 169: 733, 1952

152 RYTAND, D A. The renal factor in arterial hypertension with coarctation of the aorta J clin Invest, 17 391, 1938

153 SACHS, E, Jr, BRENDLER, S J, and FULTON, J F The orbital gyri Brain, 72: 227, 1949

154 SALDAGO, E., and SELYE, H. The rôle of the adrenals in the production of cardiovascular and renal changes by methylandrostenediol Arch int. Physiol, 62: 352, 1954

155 SAPIRSTEIN, L A, BRANDT, W L, and DRURY, D. R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water Proc Soc exp Biol. (N.Y), 73: 82, *1950.*

CHAPTER X

# THE RELATIONSHIP BETWEEN ARTERIOSCLEROSIS AND HYPERTENSION

## PATHOGENESIS OF ARTERIOSCLEROSIS, ATHEROSCLEROSIS AND ARTERIOLOSCLEROSIS

The term arteriosclerosis describes a number of interrelated pathological processes and clinical conditions. Arteriosclerotic processes in the aorta and great vessels decrease their distensibility and give rise to systolic hypertension, but the type of arteriosclerosis which gives rise to narrowing of blood vessels and may interfere with the flow through a renal artery or one of its main branches is described as atherosclerosis. The question of whether there is a renal component in the pathogenesis of essential hypertension has been referred to already. In this section it is proposed to refer briefly to our present ideas about arteriosclerosis which bear upon the problems of hypertension.

### Fibrous Replacement of Muscle and Elastic Tissue in Large Blood Vessels

With advancing years it is usually found that muscular and elastic tissue become replaced to a greater or lesser degree by fibrous tissue and the vessels may become thicker, elongated and larger in diameter. Sometimes, with the lengthening of the vessels, they become curved. In the case of the aorta, the curvature may simulate an aneurysm. The above changes are not necessarily associated with important pathological changes in the intima, but when atherosclerosis involving the intima does develop, there may be secondary calcification, and a further decrease in the distensibility of the large vessels may result. It is generally accepted tha[illegible]
vessels and thickening of [illegible]
than in normotensives. It [illegible] also by Bramwell (1924) that when the walls of large blood vessels are stretched as a result of an elevation of the blood pressure, the distensibility is decreased. Bramwell (1924) tested the elastic properties of vessels and evidence of decreased elastici[illegible]
wave velocity wh[illegible]
fore likely that [illegible] pressure is elevated from one cause, there is a further increment of blood pressure elevation brought about by the decreased distensibility of the aorta and other large vessels.

175 TURIAF, J., ZIZINE, L., and SORS, C. L'hypertension artérielle et les lésions vasculohumorales du rat en parabiose. Presse méd., 62. 57, 1954.

176 VERNEY, E. B., and VOGT, M. Observations on the effects of renal ischaemia upon arterial pressure and urine flow in the dog. Quart. J. exp Physiol., 32: 35, 1944.

177 VOLHARD, F. Die doppelseitigen haematogenen Nierenerkrankungen Springer, Berlin, p. 509, 1931.

178 WAKERLIN, G. E. Factors Regulating Blood Pressure. Transactions of the Fourth Macy Conference, *Josiah Macy Jr. Foundation*, New York, 1950.

179 WAKERLIN, G. E., CRANDALL, E., FRANK, M. H , JOHNSON, D., POMPER, L., and SCHMID, H. E. Experimental hypertension produced by constriction of the carotid sinus area Circulation Research, 2 416, 1954.

180 WAKERLIN, G. E., OSGOOD, B. G., BIRD, R. B , BRANNICK, T. L , MOORE, J. B., BURNS, R. O., HAWTHORNE, E. W., and SEVY, R. W. Treatment and prophylaxis of experimental renal hypertension with renin Factors Regulating Blood Pressure. Transactions of the Fourth Macy Conference, Josiah Macy Jr. Foundation, New York, p. 188, 1950

181 WALTER, C. W , and PIJOAN, M. J. *Persistent hypertension due to hypothalmic injury*. Surgery, 1: 282, 1937

182 WEEKS, D. M., STEINER, A., MANSFIELD, J. S , and VICTOR, J. The depressor effect of spleno-reno-pexy on hypertension due to renal ischemia J. exp. Med., 72: 345, 1940.

183 WILSON, C , and BYROM, F. B. Sustained hypertension in rats by partial occlusion of one renal artery. Lancet, 1: 136, 1939.

184 WILSON, C , and PICKERING, G. W. Acute arterial lesions in rabbits with experimental renal hypertension. Clin Sci., 3: 343, 1938

185 YEAKEL, E. H , SHENKIN, H. A., ROTHBALLER, A. B., and MCCANN, S. McD Blood pressures of rats subjected to auditory stimulation. Amer J. Physiol , 155: 118, 1948.

186 ZOLLINGER, H. U. Hypertension following experimental x-ray irradiation of one kidney in the rat. Circulation (N Y.), 5: 950, 1952

more likely to occur in atheromatous areas and may be responsible for blocking an artery.

An interesting alternative hypothesis has been advanced by Duguid (1948) who believes that following the deposition of mural thrombi on the surface of the endothelium, the small thrombus becomes covered over by a new growth of endothelium. When examined microscopically it appears that the fibrinous material has been deposited in a sub-endothelial location. Further thrombi occur and, in their turn, become incorporated in the wall by the overgrowth of endothelium. There seems to be no doubt from the work of Duguid, confirmed by Harrison (1948), that accumulations of thrombus in an artery may become altered in the course of time, so that the appearance resembles that of classical atherosclerosis. Duguid (1948) has demonstrated examples of thrombus in a coronary vessel which became organized in part, so that in section, some had all the appearance of a coronary vessel narrowed by atherosclerosis, but in an adjacent area it was manifestly thrombus.

Much interest has been taken lately in the state of lipoids and cholesterol in the blood and evidence is accumulating that the state of the lipoids in the blood may be correlated to some extent with the occurrence of arteriosclerosis. Barr (1953) finds that beta lipo proteins are increased and alpha lipo proteins are decreased *in patients with* atherosclerosis, as compared with normal people. Gofman et al. (1952) have approached the subject by a study of the movements of lipids [illegible] presence of *atherosclerosis* in man appears to be related to an increase of lipid *molecules* of higher *molecular* weight which migrate with rates of 10 to 20 Svedberg units.

In *experimental* animals hypertension seems to have little effect upon the development of spontaneous atherosclerotic lesions in large vessels[4, 11, 15, 40]. When, *however*, atherosclerosis is induced by administration of cholesterol, various forms of experimental hypertension are found to aggravate the lesions[4, 8, 31]. Even local hypertension, by maintaining an upright posture *in* rabbits, accelerated cholesterol-induced atherosclerosis[47].

Recently attention has been directed to the possibility of retarding the development of atherosclerosis *by the* administration of oestrogens. There appears to be good evidence that this occurs under experimental conditions[35, 41, 42, 43]; and the possibility that oestrogens may be effective in man has also been considered[23].

## Monckeberg sclerosis

This is a condition which appears to be unrelated to high blood pressure. It involves medium sized arteries and is associated with calcification in their walls. The process involves mainly limb arteries.

## Atherosclerosis

Atherosclerosis involves the intima of large and medium sized arteries, but small arteries are not involved. The site of election is the coronary system and this may be involved when there is little atherosclerosis in other parts of the body. The renal arteries and their larger branches may be involved in man, leading sometimes to a Goldblatt type of hypertension.

The disorder probably involves a disturbance of lipoid metabolism and there is good evidence that the extent to which atherosclerosis occurs in man is related to diet, being much less in communities where the fat content of the diet is very low Keys (1953) has reported his observations in Spain where the fat content of the diet of much of the population is well below that in the United States or Great Britain. The incidence of coronary disease and the mortality from cerebral vascular disorders and hypertension seem to be much below those in communities with a luxurious dietary. Observations were also made in Italy by Keys (1954) and by White (1954) where similar results were obtained. They noted, comparing the cities of Naples and Bologna, that the incidence of atherosclerosis, as judged by the incidence of coronary disease and cerebral vascular accidents, was higher in Bologna than in Naples, and that the fat content of the diets in Bologna is also higher than in Naples. Observations have also been made during the war years that, in countries where there was a substantial decrease in the availability of fat, the incidence of atherosclerosis decreased The literature concerning war time changes and variations in the incidence of atherosclerosis is reviewed by Katz and Stamler (1953).

There is a high incidence of coronary disease and other forms of atherosclerosis in New Zealand. The fat content of the diet is high in New Zealand [17]. There may be some relationship.

One suggestion is that atherosclerosis begins with a deposition of lipoid material beneath the intima, causing the intima to project into the arterial lumen. In this region there is local fibrosis and an increase in the vascularity of the intima, associated sometimes with minute haemorrhages. In the course of time the accumulated material in the [illegible] leaving an [illegible]

[illegible]

sometimes obliterate the lumen of a vessel. Thrombosis formation is

more likely to occur in atheromatous areas and may be responsible for blocking an artery.

An interesting alternative hypothesis has been advanced by Duguid (1948) who believes that following the deposition of mural thrombi on the surface of the endothelium, the small thrombus becomes covered over by a new growth of endothelium. When examined microscopically it appears that the fibrinous material has been deposited in a sub-endothelial location. Further thrombi occur and, in their turn, become incorporated in the wall by the overgrowth of endothelium. There seems to be no doubt from the work of Duguid, confirmed by Harrison (1948), that accumulations of thrombus in an artery may become altered in the course of time, so that the appearance resembles that of classical atherosclerosis. Duguid (1946) has demonstrated examples of thrombus in a coronary vessel which became organized in part, so that in section, some had all the appearance of a coronary vessel narrowed by atherosclerosis, but in an adjacent area it was manifestly thrombus.

Much interest has been taken lately in the state of lipoids and *cholesterol in the blood* and evidence is accumulating that the state of the lipoids in the blood may be correlated to some extent with the occurrence of arteriosclerosis. Barr (1953) finds that beta lipo proteins are increased and alpha lipo proteins are decreased in patients with

Gofman et al. (1952)
movements of lipids
of various molecules
under centrifugal forces have been classified in Svedberg units. Gofman et al. find that the presence of atherosclerosis in man appears to be related to an increase of lipid molecules of higher molecular weight which migrate with rates of 10 to 20 Svedberg units

...of cholesterol, various forms of experimental hypertension are found to aggravate the lesions [4, 8, 21]. Even local hypertension, by maintaining an upright posture in rabbits, accelerated cholesterol-induced atherosclerosis [47].

Recently attention has been directed to the possibility of retarding the development of atherosclerosis by...

## EVIDENCE THAT IN ESSENTIAL HYPERTENSION BLOOD PRESSURE ELEVATION SOMETIMES PRECEDES THE DEVELOPMENT OF ARTERIOSCLEROSIS AND ARTERIOLOSCLEROSIS

In the so-called "prehypertensive" stage, with moderate and often transient blood pressure elevations, it is not possible to exclude some as yet unspecified pathological cause for the raised blood pressure, but the youth of many prehypertensives, and the absence of appreciable positive evidence, appear to render primary arteriosclerotic changes an unlikely explanation.

The youth of some hypertensive patients is not by itself strong evidence of the absence of a primary arteriosclerosis unless full autopsy findings are available, for narrowing of the aorta and main renal vessels due to arteriosclerosis has occured in quite young children who have died from hypertension (Chapter VI), and might be present to a lesser degree in some young people who survive. Biopsy studies in such cases will usually reveal normal renal histology of the kidney with a narrow renal artery. Goldblatt has pointed out the need for careful study of all vessels, including deep seated intrarenal branches of the main renal artery. The histological study of renal parenchyma, by itself, is insufficient evidence of a normal renal circulation.

While it seems likely that disease of the larger intrarenal arteries may have been overlooked sometimes, there is a consensus of opinion that arteriolosclerosis may be absent or minimal in the early stages of essential hypertension.

Cases of essential hypertension in which the kidney taken at autopsy was normal have been reported by many authors (Pal, 1919; Bell and Clawson, 1928; Moritz and Oldt, 1937; Fishberg, 1939; Garreton-Silva, Rodriguez and Aspillaga, 1941), although most of them regarded this as an exceptional finding. When, however, cases are selected deliberately from patients in the early stages of the disorder, normal kidneys, or those showing minimal changes, are said to be encountered frequently (von Monakow, 1920; Wallgren, 1922). Thus kidney samples from early cases, removed at biopsy in the course of sympathectomy operations by Castleman and Smithwick (1943) have shown few of the findings characteristic of the more advanced cases encountered at autopsy. The temporary nature of the blood pressure rises in the early phases of the disorder also suggests that an established humoral mechanism is not operating at this early stage. Heptinstall (1954) also found minimal renal changes in 30 out of 50 renal biopsies from patients undergoing sympathectomy for hypertension.

Scott (1944) and Goldblatt (1947) criticized Castleman and Smithwick (1943) on the ground that their biopsy samples were too small and were not a fair index of the state of the kidneys from which they were

removed. It should be pointed out, however, that Smithwick's histological observations are supported by the finding of almost normal diodrast excretion, which corresponds with results published by Page and Corcoran (1945). In histological observations on postmortem material collected from moderate hypertensives under the age of 40, and dying of unrelated disorders, my observations suggest that recognizable defects in arterioles may be lacking. Where arteriolar changes were found they were much less in degree than those exhibited by the arterioles of elderly normotensives. My observations, however, did not include a proper examination of the large renal artery branches.

Cox and Dock (1941) perfused kidneys of essential hypertension cases and non-hypertensive controls and found the flow through the kidneys decreased with age, the decrease being but little greater with essential hypertension kidneys than with control kidneys from the same age group Kimmelstiel (1933), perfusing kidneys with saline, found little vascular obstruction in many early cases of benign hypertension with equal or greater vascular obstruction in some elderly normotensives. McGeorge (1945) demonstrated a decrement in the renal function with increasing age and pointed out that the renal function of young hypertensives was similar to that of young normotensives and both exhibited a better capacity to concentrate urea and chloride simultaneously (Smirk, 1933) than either old normoten-

[illegible]

... that the decrements in renal function with advancing years observed by McGeorge in normotensives and in essential hypertensives are due largely to decrease with age in the blood supply to the kidneys. The absence of any deficiency of renal function in the young hypertensive as compared with the young normotensive corresponds with the finding that histological evidence of vascular change may be trivial in the young hypertensive and much less in degree than that encountered in elderly [illegible]

Indeed, it would seem th[illegible] pathology, microscopical p[illegible] kidneys, biopsy studies of [illegible] kidneys, and renal function tests of various kinds suggests that the degree of [illegible] manent renal ischaem[illegible]

[illegible] pressure increases. Against this must stand the statement of Goldblatt that, in his wide experience, he has not encountered a case of essential hypertension in which evidence of interference with the renal circulation could not be found when all classes of vessels were examined.

In many patients the blood pressure does not start to rise appreciably

until after the age of 40 or 50. When the blood pressure first rises after the age of 45, pathological changes in renal arterioles of one kind or another will, almost certainly, be present before the blood pressure increase has reached the level ordinarily regarded as abnormal. It is possible, therefore, that in some at least of the cases in which the blood pressure begins to rise appreciably for the first time in middle life, the renal ischaemia may have initiated the increase.

## EVIDENCE THAT HYPERTENSION ACCELERATES AND PERHAPS SOMETIMES CAUSES *THE DEVELOPMENT OF ARTERIOSCLEROSIS* AND ARTERIOLOSCLEROSIS

The question of whether hypertension accelerates or causes arteriosclerotic and arteriolosclerotic changes in blood vessels is of fundamental importance.

In the larger vessels of well established cases of essential hypertension, hypertrophy of the media is encountered. In high blood pressure of varying clinical types, essential hypertension, glomerulonephritis, pyelonephritis, polycystic kidneys, medullary hyperadrenia, cortical hyperadrenia, and in experimental hypertension of different types, the typical *thickening in the walls of arterioles have been described.* Such changes may occur even in young children with hypertension of various origins. It seems that this hypertrophy also is due to the effect of increased pressure on the walls of blood vessels. At a later stage there may be atrophy of the media with fibrous replacement.

Although the vast majority of observations strongly favours the idea that high blood pressure can cause hypertrophy of the walls of arterioles and of larger arteries, a certain amount of evidence is either opposed to or fails to support this idea. In coarctation of the aorta it is stated (Graybiel, Allen and White, 1936) that the arterioles in muscle samples taken in the upper part of the body showed no hypertrophy when compared with muscles taken from the lower part of the body. On the other hand arteriolar hypertrophy in coarctation cases has been reported (Heyer and Keeton, 1941). Again there are a number of instances in the literature of high blood pressure of appreciable duration with few changes in the arterioles. In experimental hyperten- [illegible]

[illegible]

Pickering, 1937—8; Wilson and Byrom, 1939) Negative [illegible] or that

[illegible]

that the dog often can tolerate prolonged experimental [illegible] without exhibiting substantial arteriolar changes.

In addition to muscular hypertrophy, large, medium and small arteries and arterioles may show considerable reduplication of the internal elastic lamina and thickening of the intima. In large and medium sized arteries the changes are similar to those which occur with great frequency in elderly normotensives and occasionally in younger individuals. The extent of the lesions is usually greater in hypertensives than in normotensives. The increased rigidity of the aorta and other large vessels must be accepted as responsible in part for systolic hypertension in elderly persons. There seems no reason to doubt that, in man, when arteriosclerotic lesions involve one or both main renal arteries, and narrow the lumen as the result of intimal thickening, they may cause substantial hypertension. In arterioles and small arteries (e.g. interlobular in the kidney) intimal hypertrophy may cause obstruction of the lumen and lead to loss of renal parenchymal tissue. Elastic tissue hypertrophy may be considerable. In the afferent vessels to glomeruli, and to a lesser extent in other small arterial vessels, there may be a sub-endothelial accumulation of hyaline material. In malignant hypertension medial necrosis of arterioles is usually found and there may be a cellular thickening of the intima — the so-called "onionskin" appearance. Wilson and Byrom (1939, 1941) showed in the rat, that high blood pressure induced by ischaemia of one renal artery may lead to typical changes in the arterioles of the non-ischaemic kidney

Leadbetter and Burkland (1938) and Manners (1951) [illegible]

[illegible] showed the changes of malignant hypertension.

In almost every muscular organ an increase in work beyond the physiological range by any kind of muscle — cardiac, voluntary or involuntary, leads to hypertrophy. The cardiac hypertrophy in hypertension and the development of voluntary muscles with physical labour are well known In the alimentary, urinary, and biliary tracts partial obstruction leads to hypertrophy of the muscle behind [illegible]

Vascular [illegible]

by the bi[illegible]

hypertrop[illegible] [illegible] pressure in arteriovenous aneurysm, the portal veins in cirrhosis of the liver, and the great systemic veins in congestive heart failure (Pei-Lin Li, 1940).

That high blood pressure gives rise to medial hypertrophy in the smaller arteries and in arterioles may be regarded as proved. Medial fibrosis also occurs in these vessels. There [illegible]

[illegible] result of increased intravas[illegible] The literature is summarized by Hueper (1944). The

arteriolar changes secondary to high blood pressure are usually more pronounced in the kidneys than in other organs.

## COMMENT

There is no doubt at all that advanced atherosclerosis may develop in normotensive persons; and that atherosclerosis involving one or both main renal arteries may cause hypertension (Chapter VI). The relationship of these clear-cut cases to essential hypertension is another matter.

The evidence that, in its early stages, essential hypertension may be unassociated with renal ischaemia is strong, but not conclusive.

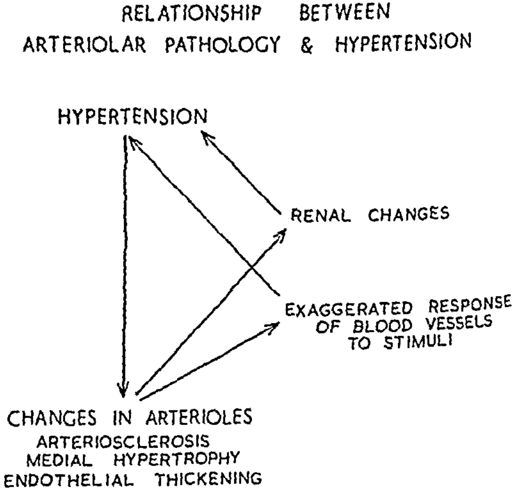



Fig X 1

Whereas many authors claim that some kidneys were normal, Goldblatt points out that large vessels may be obstructed without obvious alteration in the renal parenchyma or in the peripheral arterioles. There seems to be very little doubt from the work of Byrom and Dodson (1949) that hypertension or unilateral disease in the rat can induce

changes in the remaining kidney, which are capable of maintaining a blood pressure elevation. The evidence of such an occurrence in man depends largely upon the knowledge that nephrectomy is more likely to be successful in unilateral renal disease when this has been of short duration. If man behaves, in this respect, as the rat, then it is likely that blood pressure rises of diverse kinds may become perpetuated by causing renal hypertension. Figure X 1 summarizes some of these relationships.

The evidence that hypertension accelerates atherosclerosis in large vessels and also renal arteriolosclerosis is good; and consistent with, but not proof of, the hypothesis that, once hypertension has arisen a vicious circle may be set up — the hypertension leading to renal ischaemia and the renal ischaemia to further hypertension. By such a hypothesis a renal hypertension of the Goldblatt type could be primary, or the same process could arise secondarily to other forms of hypertension and lead to their perpetuation or increase. But the evidence that the kidneys in essential hypertension are in fact responsible for a part of the blood pressure elevation still remains presumptive. Kidneys of elderly normotensives often present histological appearances which suggest greater degrees of ischaemia than is ordinarily betrayed by the kidneys of young hypertensives.

## References


1 Barr, D. F Some chemical factors in the pathogenesis of atherosclerosis Circulation (N Y.), 8 641, 1953.
2 Bell, E. T, and Clawson, B J. Primary (essential) hypertension — A study of four hundred and twenty cases. Arch Path (Chicago), 5: 939, 1928
3 Bramwell, J C. Arterial elasticity in man Quart J Med [illegible]
4 [illegible]
5 [illegible], and Dodson, L F The mechanism of the vicious circle in chronic hypertension Clin Sci, 8· 1, 1949.
6 Castleman, B, and Smithwick, R H The relation of vascular disease to the hypertensive state — Based on a study of renal biopsies from one hundred hypertensive patients J. Amer. med. Ass, 121: 1256, 1943.
7 Cox, A J., Jr, and Dock, W The capacity of the renal vascular bed in hypertension J exp Med, 74: 167, 1941.
8 Dill, L. V, and Isenhour, C. E Occurrence of atheroma in the aorta in rabbits with renal hypertension. Arch Path. (Chicago), 33: 655 1942
9 Duguid, J B Thrombosis as a factor in th[illegible]
10 [illegible]
11 [illegible] hypertension and nephritis Lea and Febiger, Philadelphia 1939
12 Garreton Silva, A, Rodriguez, A, and Aspillaga, A. Las lesiones anatómicas de la arteria renal y de los vasos intrarrenales en relación con el fenómeno de Goldblatt-Houssay. Rev. méd Chile, 69: 629, 1941.

13 GOFMAN, J. W., JONES, H. B, LYON, T. P., LINDGREN, F., STRISOWER, B, COLMAN, D., and HERRING, V. Blood lipids and human atherosclerosis Circulation (N.Y.), 5: 119, 1951.
14 GOLDBLATT, H. The renal origin of hypertension. Physiol. Rev., 27: 120, 1947.
15 GOLDBLATT, H., KAHN, J. R., and LEWIS, H. A. Studies on experimental hypertension XIX. The production of persistent hypertension in sheep and goats J exp. Med., 77: 207, 1943.
16 GRAYBIEL, A., ALLEN, A. W., and WHITE, P. D. A histological study of the arterioles of the muscle and skin from the arm and leg in individuals with coarctation of the aorta J. clin. Invest., 14: 52, 1935.
17 GREGORY, E., JACKSON, P R, CHAMBERS, E. C., and MCLAUGHLIN, E. C. G I. Dietary studies of one hundred and seventy families of varying occupations. N. Z. med J, 42: 64, 1943.
18 HAMPERL, H., and HELLER, H. Die Organveränderungen bei experimentellem Dauerhochdruck. Arch. exp. Path Pharmak., 5: 517, 1934
19 HARRISON, C V. Experimental pulmonary arteriosclerosis J. Path. Bact, 60: 289, 1948.
20 HEYER, H. E., and KEETON, R. W. Arteriolar changes of skeletal muscle in patients with hypertension of varied origin. Amer. J clin. Path, 11: 818, 1941
21 HEPTINSTALL, R H. Renal biopsies in hypertension Brit Heart J., 16: 133, 1954
22 HUEPER, W. C. Arteriosclerosis. Arch Path (Chicago), 38: 245, 1944
23 KATZ, L. N., and STAMLER, J. Experimental atherosclerosis. Charles C Thomas, Springfield, Illinois, 1953
24 KEYS, A Atherosclerosis — A problem in newer public health J Mt Sinai Hosp, 20: 118, 1953
25 KEYS, A. Symposium — Atherosclerosis Second World Congress of Cardiology, Washington D. C, 1954
26 KIMMELSTIEL, P Benigne Nephrosklerose und arterieller Hochdruck Virchows Arch path. Anat, 290. 245, 1933
27 LEADBETTER, W F, and BURKLAND, C. E. Hypertension in unilateral renal disease J Urol. (Baltimore), 39: 611, 1938
28 MCGEORGE, M. Renal function and prognosis in benign hypertension Quart. J Med, n s 14 171, 1945
29 MANNERS, T Unilateral malignant nephrosclerosis in a child J Path Bact, 68 63, 1954
30 MORITZ, A R, and OLDT, M R Arteriolar sclerosis in hypertensive and non-hypertensive individuals Amer J Path, 13: 679, 1937
31 MOSES, C Development of atherosclerosis in dogs with hypercholesterolemia and chronic hypertension Circulation Research, 2. 243, 1954
32 PAGE, I H, and CORCORAN, A C Arterial hypertension: Its diagnosis and treatment The Year Book Publishers Inc, Chicago, 1949
33 PAL, J Über Herzhypertrophie und Hypertonie Med Klin, 15. 662, 1919
34 PEI LIN LI Adaption in veins to increased intravenous pressure, with special reference to the portal system and inferior vena cava J Path. Bact, 50 121, 1940
35 PICK, R, STAMLER, J, RODBARD, S, and KATZ, L N. The inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks. Circulation (N Y), 6: 276, 1952
36 SCOTT, R W Criticises Smithwick's biopsies Arch Surg (Chicago), 49 192, 1944
37 SHAW, A. F. B., and GHAREEB, A A The pathogenesis of pulmonary schistosomiasis in Egypt with special reference to Ayerza's disease J. Path Bact., 46 401, 1938.

38 Smirk, F. H Chloride and urea excretion as a measure of the functional activity of healthy and diseased kidneys Clin. Sci, 1: 131, 1933
39 Smithwick, R. H, Wilkins, R, Levene, G, Whitelaw, G. P, Kinsey, D, Thompson, J E, and Greer, W. Hypertensive cardiovascular disease Methods of study and treatment Massachusetts Medical Society, Boston, May, 1952.
40 Stamler, J, Katz, L. N., and Rodbard, S. Serial renal clearances in dogs with nephrogenic and spontaneous hypertension J. exp Med, 90. 511, 1949
41 Stamler, J, Pick, R, and Katz, L N. Prevention of coronary atherosclerosis by estrogen-androgen administration in the cholesterol-fed chick. Circulation Research, 1: 94, 1953
42 Stamler, J, Pick, R., and Katz, L N. Estrogen prophylaxis of cholesterol-induced c[illegible]
ACTH C[illegible]
43 Stamler, J. [illegible]
coronary [illegible]
10: 251, [illegible]
44 von Monakow, P. Blutdrucksteigerung und Niere. Dtsch. Arch klin. Med, 133: 129, 1920.
45 Wallgren, A Die Arterien der Niere und der Blutdruck Acta med scand, *56, 356, 1922*
46 White, P. D. Cardiovascular epidemiology. Second World *Congress of* Cardiology, Washington D C., 1954
47 Wilens, S. L The effect of postural hypertension on the *development of* atheromatosis in rabbits fed cholesterol. Amer. J. Path, 19: 293, 1943
48 Wilson, C, and Byrom, F. B Renal changes in malignant hypertension Lancet, 1: 136, 1939
49 Wilson, C, and Byrom, F. B The vicious circle in chronic Bright's disease — Experimental evidence from the hypertensive rat Quart. J Med, n s 10: 65, 1941
50 Wilson, C, and Pickering, G W Acute arterial lesions in rabbits with experimental renal hypertension Clin Sci, 3: 343, 1937—38

CHAPTER XI

# PATHOGENESIS OF ESSENTIAL HYPERTENSION

The condition we describe as essential hypertension is recognizable as a clinical syndrome, and there is much discussion as to whether the syndrome can be explained in terms of a single pathology or whether it is the manifestation of a group of disorders which we have not as yet the means to differentiate. The author's preference (Smirk, 1949) is for a third possibility which will be described in some detail, namely, that the rise of blood pressure signals the first emergence of essential hypertension as a separate clinical entity; being as it were the point at which many contributing streams join to make a recognizable river (Fig. XI 1). In terms of this view, substantially all of the clinical manifestations of essential hypertension are secondary to the raised blood pressure or excessive vasoconstriction. Whatever underlying pathological processes have given rise to the blood pressure elevation in essential hypertension, they do not (excepting those which are psychogenic) give rise to clinical manifestations, their adverse influence being made known to us only through the intermediation of the blood pressure elevation. There are, however, many disorders which have elevation of the blood pressure as but one of their clinical manifestations, for example, nephritis, Cushing's syndrome, pyelonephritis, congenital cystic kidney and aortic coarctation. Such conditions have clinical features by which they are recognizable as disorders separable from essential hypertension; but in so far as they have blood pressure elevation, they may and do exhibit any or all of the clinical manifestations of the syndrome of essential hypertension. Elevated blood pressure plays its part as a secondary cause for clinical manifestations in these conditions, in very much the same way as it does in essential hypertension.

Essential hypertension looked at in this way is a condition not unlike obesity. We may point to patients who are recognizably thin or abnormally fat, but it is arbitary to define a level of body weight, above it being abnormal and below it normal. So it is in hypertension. At higher levels of the blood pressure clinical manifestations are more likely to appear and at lower levels they are less likely to appear. There does not seem to be any pressure which demarcates the boundary

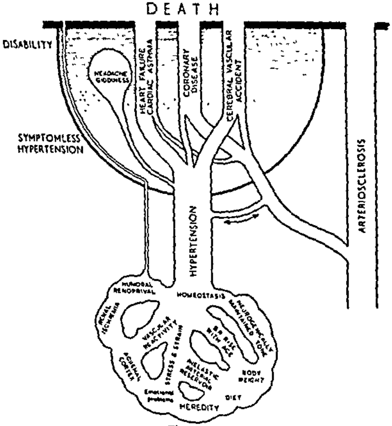



Fig. XI 1

The figure summarises the author's concept of the pathogenesis of essential hypertension. Disability and eventual death *from* this disorder are due to conditions which are secondary to or accelerated by the hypertension The chief associated ... arteriosclerosis (using the term ... cause of arterio...

contributes varies from ...
diagram as causes of d...

Some of the primary causes of hypertension are represented in the diagram as contributing (and inter-communicating) channels which lead into ... When the common channel is ... intended ... of sever... connect... factors ... contrib... Heredit...

| | |
|---|---|
| Heredity | ... physiological "set" of blood pressure level, i e whether it is adjusted homeostatically to a higher or lower level |
| Heredity | — Obesity. |
| Obesity | — Disposition to atheroma |
| Diet | — Disposition to atheroma. |
| Diet | — Disposition to atheroma. |
| Age | — Obesity. |
| Atheroma | — Disposition to atheroma |
| Atheroma | — Inelasticity of arterial reservoir. |
| Renal ischaemia | — Renal ischaemia. |
| Renoprival-like state | — Increased vascular reactivity to pressor stimuli. |
| Overaverage activity of the adrenal cortex | — Increased vascular reactivity to pressor stimuli. |
| | — Increased vascular reactivity to pressor stimuli. |

between abnormal and normal, and although arbitrary distinctions may be made for the purposes of life insurance, or for some of the purposes of clinical medicine, they lack status in a discussion on pathogenesis.

If the height of the blood pressure as such, or the vasoconstriction present, leads to clinical manifestations, then so far as the patient's syndrome is concerned, it seems likely that it is a matter of indifference whether the blood pressure elevation is produced by the simple overaction of physiological processes (by a person being as it were at the upper end of a normal distribution curve: Smirk, 1949, Pickering, 1955) or whether the blood pressure, starting initially at a lower level, has been elevated to the same degree as a result of a pathological process. While recognising that the borderline between "physiological" and "pathological" is sometimes indefinite, the present author's preference is for the view that both "physiological" and "pathological" factors contribute to the development of the disorder essential hypertension.

Acceptance of this hypothesis leads to a far-reaching conclusion, namely, that in seeking to trace the full development of the disorder, we must evaluate the contributions made by many factors rather than seek for a single explanation.

Thus any change in any part of the circulatory system which causes a lasting rise of pressure (or excessive vasoconstriction) is likely to accelerate the development of hypertensive manifestations, and anything which lowers the blood pressure retards these deteriorations. If anything which induces a lasting rise of the blood pressure is concerned in the pathogenesis of hypertensive disease, then the rise of blood pressure with age, certain hereditary traits, obesity and arteriosclerosis may be set down as among the known causes of blood pressure elevation. It will be our task to examine the various factors which raise the blood pressure and attempt to understand the mechanism and to estimate their importance. It will be all too evident that there are important gaps in our knowledge.

The subject of pathogenesis is necessarily complex and the author suggests, with some diffidence, that readers who can afford the time read the preceding chapters first; and before turning to the detail of this chapter, read the summing up and spend time on Figs. XI 1–4.

## EVIDENCE THAT CLINICAL MANIFESTATIONS OF ESSENTIAL HYPERTENSION ARE CAUSED BY ELEVATION OF THE BASAL BLOOD PRESSURE

Certain clinical manifestations appear to be secondary to high blood pressure because they are encountered in all of the disorders characterized by blood pressure elevation

The clinical manifestations to which reference is made include

congestive heart failure, cardiac asthma, breathlessness on exertion of cardiac origin, electrocardiographic changes characterized by left ventricular preponderance and increases in heart size. There are retinal manifestations including papilloedema, retinal oedema, soft exudates, hard exudates (stellate figures) and haemorrhages; and changes in the blood vessels such as waistlike narrowings of arteries and nipping of the arteriovenous crossings. Headaches, giddiness, attacks of encephalopathy and epistaxis also occur in hypertension irrespective of the primary cause. Cerebral vascular accidents are more frequent when hypertension is present, but they also occur frequently when the blood pressure is normal. Patients will of course differ in their vulnerability to the effects of blood pressure elevation.

The fact that these clinical manifestations are related to the elevation of the blood pressure is indicated also by the fact that reduction of the blood
magnitude
in such o
(Chapter XXI). This improvement is independent of the cause of the blood pressure elevation. Although the various methods of therapy are unequal as regards their efficiency, the character of the improvements induced do not differ from one form of therapy to another. Thus reduction of the blood pressure by ganglionic blockade with or without reserpine, by veratrum alkaloids, surgical sympathectomy, adrenalectomy, rice diets and other substantial salt depletions, when they are effective, cause improvements of the same kind, though differing in the degree of relief

Whereas most methods are effective in reducing the blood pressure and relieving manifestations in only a certain proportion of cases, ganglionic blockade causing blood pressure reduction of sufficient degree and duration relieves hypertensive manifestation in almost all patients, irrespective of aetiology.

It is unfortunate not only for
but also for the better understa
issue of the effects of drug therap
of inadequate techniques of control and administration.

Most writers attach less importance to transient blood pressure elevations than to fixed rises of blood pressure. When, in a series of hypertensive patients, we studied the relationship between the clinical manifestations and the levels of the supplemental and basal blood pressures taken at the same time (Smirk, Alstad, Kilpatrick and Veale, 1956),
was closely re
substantially
of the height of the supplemental blood pressure In addition, we found in an 8-year follow-up that the mortality of untreated cases (adjusted for age) showed a strong positive

correlation with the height of the basal pressure and a slight negative correlation with the height of the supplemental pressure.

It is not surprising that the basal pressure should bear the closer relationship to clinical manifestations, but the absence of any obvious relationship to the supplemental pressure was unexpected. It should be remembered, however, that the supplemental pressure referred to is the casual blood pressure at a routine visit of the patient to the clinic minus the basal blood pressure. This supplemental pressure which represents the patient's response to the clinic environment, proves to be neither an indication of the severity of the disorder at the time the pressure is measured nor of the future prospects of the patient. This does not mean however, that all other supplemental pressures — representing the patient's responses to his usual environment (away from the clinic) — are unimportant. Investigations on pathogenesis must, nevertheless, take account of the fundamental differences between basal and supplemental pressure.

If one and the same basic pathology were responsible for causing elevation both of basal and supplemental pressures, one might expect that in a series of hypertensives there would be a positive correlation between the degrees of elevation of the basal and supplemental pressures. But the reverse is true.

The fact that rises in the basal and supplemental pressures are not positively correlated, and that there is even a negative relationship, suggests strongly that there is more than one factor responsible for elevation of the casual blood pressure (Veale et al., 1956), (Chapter III). Indeed, it is almost as if elevation of the casual blood pressure is a statistical coincidence which takes place when a person who has a high basal pressure also exhibits a high supplemental blood pressure (Smirk, 1944; 1949).

The slight negative relationship between supplemental and basal pressures may be due to the operations of homeostasis It may, however, be due to experimental error If a patient does not come down to a true basal level the pressure recorded as basal will be a little higher and the calculated supplemental pressure a little lower than the true value. The error will always be in the direction of overestimating the basal and underestimating the supplemental If true basal and supplemental pressures were independent variables, the occurrence of such an error would lead to a negative correlation of the pressures as recorded

## Comment

There is strong evidence that the clinical manifestations associated with essential hypertension are due to elevation of the basal blood pressure, and that elevation of the supplemental blood pressure does not ordinarily lead to important clinical manifestations.

The characteristic clinical manifestations of essential hypertension can all be explained as secondary to hypertension. It seems, therefore,

that most of the basic causes of essential hypertension elevate the blood pressure but are otherwise harmless. (It is possible, however, that if death from hypertension is sufficiently postponed the basic pathology may be found to give rise to clinical manifestations other than hypertension — the one I have in mind is uraemia).

## PRIMARY CAUSES OF BLOOD PRESSURE INCREASE

Many authors have laid emphasis on the probability that several pathogenic factors may be concerned in causing the elevation of the blood pressure in essential hypertension (Volhard, 1948; Fishberg, 1954; Corcoran et al., 1951; Oehme, 1951; Arnold, 1952; Schroeder, 1953; Smirk, 1946, 1949; Pickering, 1955). The subject of pathogenesis is made more complicated by the inter-relationships which exist between a number of the factors which are evidently concerned in some way with blood pressure elevation. There must be a stage at which there are primary causes which lead to blood pressure elevation, and it is suggested that there is also a secondary stage in which hypertension leads to functional and structural changes which perpetuate the blood pressure rises and may cause further increases. It will be convenient to subdivide the subject into factors which initiate blood pressure rises, and those which are secondary to the initial rises of blood pressure (and may, on occasion, set up a vicious circle). The factors referred to in this section as certainly, or as probably, concerned in starting the blood pressure rise, may be divided into those which are constitutional (endogenous) and those which are environmental.

### Constitutional Causes for Blood Pressure Elevation

A complex inter-relationship exists between the various constitutional causes as will be evident from the following Figure.

There is very good evidence that relationships exist between elevation of the blood pressure (not necessarily of the highest order) and heredity (Chapter III), age (Chapter III), obesity (Chapter III), arteriosclerotic changes (Chapter X), tenseness of disposition (Chapters IV and VII), and probably constitutional differences in the reactivity of blood vessels to stimuli. As indicated in the Figure, heredity, age, obesity etc. are not altogether separate factors. Thus, heredity probably influences the particular state of physiological equilibrium which decides whether a blood pressure will be in the higher or lower physiological range. Heredity probably influences the rate with which the blood pressure rises with age, the incidence of obesity, the disposition to develop arteriosclerosis and probably the disposition to tenseness and over-alertness. It is not unlikely that heredity influences the differences in the degree of reactivity of the

individual to pressor stimuli and the capacity of the heart and blood vessels to withstand an overload.

The disposition of the blood pressure to rise with age may be partly physiological. But age also influences the occurrence of obesity and of arteriosclerosis; and since obesity and arteriosclerosis may be associated with elevation of the blood pressure, there may be three ways in which advancing age elevates the blood pressure.

POSSIBLE CONSTITUTIONAL CAUSES OF RAISED BLOOD PRESSURE

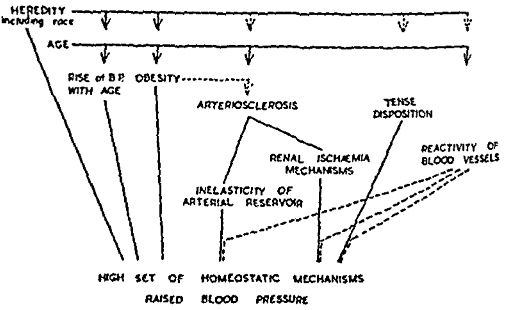



Fig. XI 2

Heredity probably influences several mechanisms which affect the blood pressure level. In some instances the evidence is speculative, e g that the tendency to arteriosclerosis is inherited The arrows made with dotted lines indicate the more speculative suggestions The relationship between age and hypertension may also depend on several distinct processes which are more liable to occur in older people, such as the occurrence of obesity, of arteriosclerosis and of a state in which the reactivity to pressor stimuli is increased. There are at least two mechanisms by which arteriosclerosis may cause a degree of elevation of the blood pressure

Reactivity of the blood vessels, or of the blood vascular system as a whole, can be shown to vary from one individual to another. It may be supposed that those individuals who can be demonstrated to be more reactive to certain pressor stimuli may also over-react to other stimuli which are concerned in blood pressure elevation. There is evidence that the reactivity of the blood pressure to stimuli varies considerably from one individual to another (Doyle and Smirk, 1955. Chapter VIII). Therefore, a disposition of the blood vessels, or of the blood vascular system as a whole, to react more vigorously than usual might be the

means whereby a stimulus, which would not ordinarily carry the blood pressure level into the abnormal range, succeeds in doing so.

In the diagram I have indicated the close relationship between a high level of operation of the homeostatic mechanisms and raised blood pressure, because these anomalies are rarely dissociated. With the few exceptions referred to in Chapter XVIII there is evidence that whatever the cause of the hypertension, there is *pari passu*, a rise in the level at which the homeostatic mechanisms operate; and in nephritis, Cushing's syndrome, essential hypertension, malignant hypertension and so forth, the homeostatic mechanisms may be demonstrated to react against both rises and falls of blood pressure. In this connection I have used the terms "neurogenically maintained" and "not-neurogenically maintained" because it is difficult to distinguish between:

1 An increase in the number of nerve impulses discharged from the central nervous system.

2. The extent to which preganglionic impulses influence the discharge from ganglia.

3 The extent to which postganglionic influences affect the discharge of chemical transmitters at nerve endings, and

4 The degree to which the muscle of blood vessels responds to the stimulus it receives.

The term "neurogenically maintained" designates that part of the blood pressure which is dependent on nerve impulses without distinguishing between the effect of an increase in the number of nerve impulses leaving the central nervous system and an increase in the reactivity of ganglia, nerve terminals or blood vessels. The expression has the additional advantage that it takes account of the responses of the heart and of the effect of the homeostatic mechanisms. The expressions "neurogenically maintained" and "not-neurogenically maintained" distinguish, therefore, between those parts of the blood pressure elevation which, when various homeostatic and other adjustments have been made, turn out to be ultimately dependent upon the discharge of nervous impulses and those which are not so dependent.

*Effect of heredity* — The influence of heredity on the incidence of essential hypertension has been discussed in [illegible]

[illegible] 1955). It has been stated that essential hypertension is inherited as a dominant with less than 100 per cent expression of the abnormality or of the abnormalities concerned, but evidence against this view has been brought forward by Hamilton et al (1954). The close relationship between the blood pressures of like twins at all levels, normotensive and hypertensive, has been referred to earlier. In general, when one uniovular twin is hypertensive, so also is the other

Unfortunately it is not known what is inherited. Even before adult years are attained, children of hypertensives tend, as an average, to have slightly higher blood pressures than the children of non-hypertensives. They are also, as an average, rather heavier in weight. It is unknown whether inheritance affects the supplemental or the basal blood pressure or both of these. It is likely (Fig. XI 2) that more than one factor influencing blood pressure elevation is inherited. Pickering (1955) draws the important conclusion that "within the upper ranges, arterial pressure behaves like a graded characteristic so far as inheritance is concerned. It seems probable, but is less securely established, that it behaves similarly throughout the range of arterial pressures In this it broadly resembles height, but the role of inheritance is here much more definite, partly no doubt because height is very much less affected by momentary variations." This conclusion appeals to me because for many years I have regarded essential hypertension as depending on "the total effect produced by the combined action of several components . . ." (Smirk, 1946, 1949). It is unlikely that contributing factors would all be subject to the same genetic influence.

Great interest attaches to the observation of Hines and Brown (1935) who reported that, among the children of hypertensives, there is an inherited tendency to exhibit overstrong reactions to the cold pressor test and for such hyperreactors to become hypertensive in later life. Unfortunately, remarkable difference exists between results obtained by various workers who have repeated the observation.

*Effect of age.* — An account of the effects of age on the blood pressure level is given in Chapter III. Population surveys of casual blood pressures in Great Britain, U.S.A. and New Zealand show a striking rise with age. The rise is influenced by, but is not dependent on, the inclusion of more frankly hypertensive individuals in the older age groups. In some eastern communities with little hypertension this rise with age does not continue after the age of 40.

When we study the relationship between age and the levels of the basal and supplemental pressures (Veale et al., 1956) we find that the rise in the casual blood pressure with advancing years involves a rise in both basal and supplemental components, in the sense that a group of old people may be expected to have mean values for the basal and supplemental pressures both of which are higher than the mean values for a group of young people. In our survey we found that the rate of increase of the blood pressure also increased with age.

The behaviour of the mean blood pressure of a population and of the mean rate of increase of the blood pressure must not be confused with the behaviour of the individual. We made an additional survey of a hospital population in which records of the blood pressure extended over periods up to and exceeding fifteen years (Chapter III). In the course of the fifteen years we found rises of blood pressure occurred in

40 out of 49 patients. It was also found that the rate of increase of the blood pressure varied enormously. Although the majority of individuals show a rise with age, the attainment of frankly hypertensive levels may take place within a few years. It is not unusual for patients to rise from well below the mean blood pressure for their age to well above this level within fifteen years. Patients who are below the mean pressure for their age in the fourth or fifth decade may yet attain frankly hypertensive levels.

[illegible]

contributing causes for essential hypertension.

Among the factors which may be in part responsible for the blood pressure elevation with advancing years are: decrease in the distensibility of the arterial reservoir, thus causing systolic hypertension, arteriosclerotic processes involving the kidney, increase in the reactivity of the blood vessels brought about by work hypertrophy, increase in the reactivity of the blood pressure to certain stimuli as an ageing phenomenon (Alam and Smirk, 1938; Pickering and Kissin, 1936) and a higher operating level of the homeostatic regulating mechanism.

*Effect of obesity.* — It is clear that overweight is associated with a tendency to higher blood pressure levels and in the due course of time to a higher incidence of [illegible]
average w[illegible]
tendency [illegible]
balance o[illegible] suggests that the positive correlation between overweight and elevated blood pressure is still present when allowance has been made for errors in blood pressure measurement by cuff methods, due to upper arm obesity.

Veale, Irvine and Hamilton (1956) find evidence in our New Zealand survey that basal and supplemental pressures are positively correlated with obesity [illegible]

X[illegible]

Su[illegible] blood pressure increase in two ways (Fig. XI 3)

1. Arteriosclerosis causes a decrease in the elasticity of the arterial reservoir and may lead to a moderate rise of blood pressure, mainly systolic (Bramwell, 1924, Fahr et al., 1932; Wiggers, 1938). It is sometimes stated that the mean blood pressure is not raised (Fahr et al., 1932)

2. [illegible]
to ess[illegible]
ing o[illegible]
w[illegible] arteriosclerosis may cause

large rises of blood pressure and, in unilateral cases, nephrectomy may cure the hypertension (Chapter VI). It is not known how often renal ischaemia due to arteriosclerotic changes in several branch arteries is a contributory cause of blood pressure elevation in essential hypertension. There is no doubt that renal ischaemia may cause lasting hypertension in man (Chapter VI) as well as in experimental animals

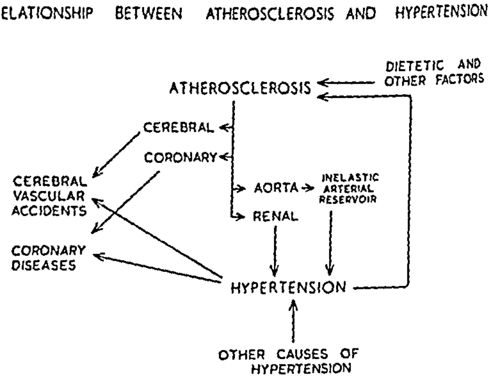



Fig. XI 3

Most of the relationships set out in the figure are based on substantial evidence, but the part played in essential hypertension by renal arteriosclerosis is not yet understood.

(Chapter IX). The mechanism, however, is still insufficiently understood. Probably liberation of pressor substances, and an effect due to decrease in the amount of normal renal tissue, both play some part. It seems likely to me that renal ischaemia plays a part in raising the blood pressure in at least some stages of essential hypertension. The observation of Kahn (1956) that purified hypertensin I has four times the pressor activity of noradrenaline, adds to the weight of evidence.

*The effect of tenseness, overalertness and other psychological traits.* — The subject has been discussed in Chapters IV and VII. Rises in supplemental pressure have been shown to occur in response to emotional stimulation of various kinds. It is uncertain whether such elevations, if sufficiently frequent or prolonged, predispose the subjects towards the development of permanent hypertension. Excessive blood pressure rises with emotion may be due to an over-reactive cardio-

vascular system. Therefore, it should not be assumed that large rises of blood pressure necessarily mean that there is excessive emotion. Examples have been given (Chapter VII) of emotional rises of blood pressure which lasted several weeks or months, even after cessation of an external cause. We made experiments on rats with audiogenic stimulation (using an orchestra of motor horns in a sound-proof auditorium). Blood pressure rises were induced which persisted for several weeks and in some instances for months after withdrawing the stimulus; they were not abolished by anaesthesia (Chapter IX). Evidently blood pressure increases outlast the stimuli which caused them.

Eastern European writers interpret essential hypertension in accordance with the ideas of Pavlov. Lachmann (1953) states that the characteristics of the nervous system of the patient must be considered in relation to the social environment. Aetiological factors include: pathological overstrain, dreams in the emotional sphere and *negative emotional influences*. These lead to loss of normalizing impulses from the cerebral cortex, leading to overexcitability of the vasomotor centres. Secondary changes may then fix the hypertension. Similar views are expressed by Gömöri (1953). Mjasnikov (1956) found that "monkeys after disturb[illegible]
dítione [illegible]
progres[illegible] hypertension. The hypertension sometimes persisted for 2 or 3 years and one monkey died of an acute myocardial infarct.

Shapiro and Horn (1955) observed moderate blood pressure rises in cats when attempts were made to induce an experimental neurosis by a negative stimulus applied in association with feeding.

*Effect of high reactivity of the cardiovascular system to pressor stimuli.*—There seems to be good evidence that there are differences in the degree of reactivity to pressor stimuli among normotensive individuals. These are not dependent on differences in the efficiency of homeostatic controls and they may reasonably be described as constitutional differences. It seems very likely that the effect of pressor agencies will be greater in persons whose cardiovascular systems react strongly than in persons who react weakly. Reference will be made later to induced changes in vascular reactivity.

*Comment* — Of the various factors mentioned under the heading of constitutional causes likely to be concerned in blood pressure elevation, the effects of heredity, age and emotional stimulation may be regarded as established though the latter [illegible]
plemental [illegible]
[illegible]
[illegible] but the evidence that increased [illegible]ity assists blood pressure elevation is based on circumstantial evidence.

large rises of blood pressure and, in unilateral cases, nephrectomy may cure the hypertension (Chapter VI). It is not known how often renal *ischaemia* due to arteriosclerotic changes in several branch arteries is a contributory cause of blood pressure elevation in essential hypertension. There is no doubt that renal ischaemia may cause lasting hypertension in man (Chapter VI) as well as in experimental animals

RELATIONSHIP BETWEEN ATHEROSCLEROSIS AND HYPERTENSION

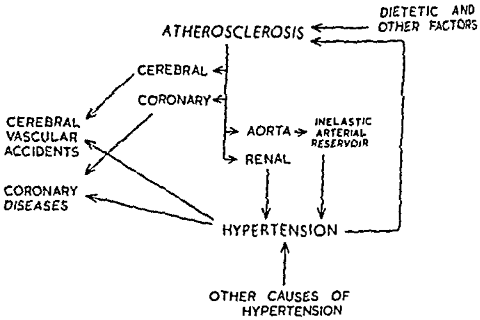



Fig. XI 3

Most of the relationships set out in the figure are based on substantial evidence, but the part played in essential hypertension by renal arteriosclerosis is not yet understood

(Chapter IX). The mechanism, however, is still insufficiently understood. Probably liberation of pressor substances, and an effect due to decrease in the amount of normal renal tissue, both play some part. It seems likely to me that renal ischaemia plays a part in raising the blood pressure in at least some stages of essential hypertension. The observation of Kahn (1956) that purified hypertensin I has four times the pressor activity of noradrenaline, adds to the weight of evidence.

*The effect of tenseness, overalertness and other psychological traits* — The subject has been discussed in Chapters IV and VII. Rises in [illegible] have been shown to occur in response to emo- [illegible] ds. It is uncertain whether such [illegible] prolonged, predispose the subjects towards the development of permanent hypertension. Excessive blood pressure rises with emotion may be due to an over-reactive cardio-

salt. It may be true that mechanized and industrialized civilizations involve more stress, strain and emotional tension than exists in pri-

hypertension is uncommon among poor people on restricted diets and common among wealthier people who enjoy diets rich in calories, fats and *proteins*. Deficiencies of diets in impoverished communities and *in wartime* may involve calories, proteins, fats, salts and vitamins. Loss of weight is commonly associated with some fall of the blood pressure, and diets deficient in calories may have some of their effect upon the mean blood pressure of a community in this way. Reduction in the intake of fat may perhaps reduce the incidence of hypertension by decreasing renal atherosclerosis.

Although a separation of the factors responsible is difficult, it appears from observations of Keys (1954) and White (1954) in Italy, that low fat diets are not only associated with the decrease in the incidence of atherosclerosis, but also with decrease in the incidence of hypertension. This occurs in communities where fats and proteins are low but calories not notably deficient.

Although the relative importance of the factors responsible has not been evaluated, there seems to be very strong evidence (Chapter III) that populations or communities where the mean blood pressure is low, even in young age groups, have a low incidence of essential hypertension and those in which the mean blood pressure of the community is relatively high have a comparatively high incidence of essential hypertension.

Quite apart from particular geographical situations it may be stated that, in general, when the statistics of communities or groups of individuals who are known to be predisposed to hypertension are compared with groups who are less predisposed, a relationship is apparent between the blood pressure levels of the community as a whole and the incidence of hypertension in that [illegible]
that the level of the blood press [illegible]
is set at a higher level in grou [illegible]
high bl[illegible]
occurs [illegible]
high i[illegible] [illegible], among students attending for health examinations and persons attending for life insurance examinations When, under wartime deprivations, the mean blood pressure of a community is reduced, so also is the incidence of essential hypertension The mean blood pressure level in the obese is higher than it is in the lean, and the incidence of essential hypertension correspondingly greater. The extent to which such observations can be made applicable to an individual is unknown.

## Environmental stimuli Tending to Induce Rises of Blood Pressure

Strong evidence has been brought forward in Chapter III that *environment in a broad sense may have an important influence on the occurrence of essential hypertension.* Environmental factors are *mentioned* as of importance by Smirk (1949) Schroeder (1953) and

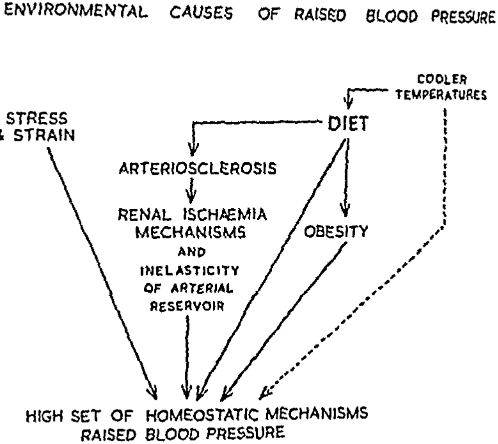



Fig XI 4

*The figure indicates some possible relationships between environmental factors and*

weight and on the development of atheroma, and by alterations in salt consumption if *these are of sufficient magnitude*

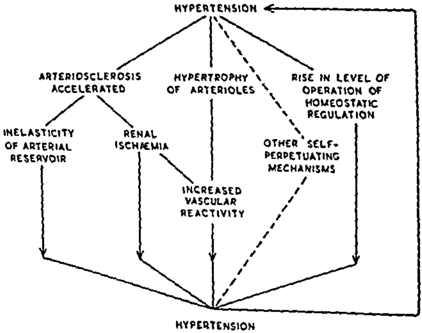
*Pickering (1955). It has proved difficult to distinguish the relative* importance of individual factors. It has been shown that some communities have a *high and others a low incidence of hypertension* (Chapter III). The summary diagram indicates the situation as it appears *to the author* at the present time.

It is difficult to distinguish between the effects of race and of such environmental *factors* as *climate, physical activities,* environmental stress and strain, and such dietetic factors as calories, proteins, fats and

### Occurrence of Enhanced Reactivity to Pressor Stimuli as a Secondary Phenomenon

Reference has been made already to the variations in the reactivity to pressor stimuli which occur in normotensives and are not dependent on (though they must be influenced by) individual differences in the efficiency of the homeostatic controls.

SELF PERPETUATING AND SELF AUGMENTING MECHANISMS




For further detail see text

Fig XI 5

McQueen has shown that renal ischaemia, as well as nephrectomy, leads to increased reactivity of perfused rat blood vessels [illegible] There is also [illegible] increased rea[illegible] the V.E.M [illegible] reactivity, see Chapter IX).

Unfortunately, it is difficult clinically to distinguish between enhanced reactivity to pressor stimuli which is constitutional and increases which have been acquired.

Changes in blood pressure are not reliable indications of changes in vascular reactivity, for blood pressure changes represent the total response, including not only the capacity of the blood vessels to alter their calibre, but also the responses of the blood pressure regulators.

It is of interest in this connection that Dahl and Love (1954), making observations on a working community, found that individuals who habitually had a low salt intake had a much smaller incidence of hypertension than those of the same community who had a high salt intake. When, however, sodium deprivation is used in therapy it is generally accepted that the sodium intake must fall to such low levels as 0.2 gm. of sodium daily before notable falls of blood pressure occur in a large proportion of patients.

The question arises whether such slight blood pressure elevations, of whatever origin, predispose to further blood pressure rises at a later date. It seems that the blood pressure level is often raised, if only to a slight degree, long before arteriosclerotic changes are likely to be prevalent.

Comparatively little attention has been given in British and American writings to a suggestion of Arnold (1949) who noted rises of blood pressure following infections of various kinds. He thinks they may be concerned aetiologically in the rises of blood pressure in essential hypertension. Proof is difficult.

## WAYS IN WHICH PATHOLOGICAL CHANGES INDUCED OR ACCELERATED BY HYPERTENSION MAY LEAD TO FURTHER ELEVATION OF BLOOD PRESSURE

The idea that hypertension may lead to pathological or functional changes which in some way perpetuate themselves, or lead to further increases of blood pressure, was promulgated by Volhard (1948); and additional evidence of self-perpetuating or self-augmenting mechanisms has become available which, unfortunately, is largely circumstantial and based on animal experiments.

The figure summarizes some of the ways in which an elevated blood pressure might cause changes which lead to further rises of blood pressure

### Arteriosclerosis

Wilson and Byrom (1941) and Byrom and Dodson (1949) considered, on experimental evidence, that hypertension causes renal artery lesions and these in turn cause further rises in blood pressure In this way a vicious circle is set up.

In man there is good evidence that hypertension accelerates arteriosclerotic processes, especially in the kidney (Chapter X), and if it be accepted that arteriosclerosis may lead to hypertension, it must be accepted also that high blood pressure is likely to promote additional rises of blood pressure. Large blood pressure increases may occur experimentally, and sometimes clinically, as the result of renal ischaemia; and small or moderate rises are likely to follow decreased elasticity of the arterial reservoir.

than in normotension, in many cases of hypertension the blood pressure is no more reactive than in normal subjects. The high reactivity to these reflexes cannot by itself explain the hypertension. In fact, Alam and Smirk (1938) found that the average level of the resting pressure, in their more reactive patients with essential hypertension, did not differ appreciably from the level of the resting blood pressure in the less reactive patients. The averages of the systolic blood pressures *at rest* in the patients with essential hypertension were 169 for those giving reflex increases of 40 mm. or more, and 171 for those giving reflex increases of less than 40 mm.

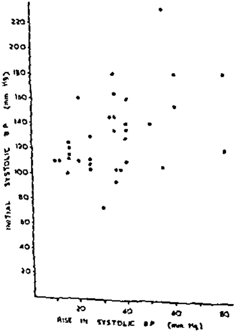



Fig XI 6b

The rise in systolic blood ...

The effect of applying two blood pressure raising stimuli simultaneously was studied by Bruce, Martin and Smirk (1945). They found with several pairs of stimuli that the sum of th...

... blood pressure rise in response ...

However, evidence of increase in the pressor response to well-defined stimuli is of importance even when it is difficult to evaluate the factors concerned.

Reference was made in Chapter VIII to the fact that, if the blood pressure is allowed to fall to near basal levels, both in the normotensive and in the hypertensive, and then the stimulus of cold to a hand is applied, the change of the blood pressure is stated to be greater in the hypertensive than in the normotensive of the same age group (Hines and Brown, 1932, 1933; Alam and Smirk, 1938; Ayman and Goldshine, 1938). Pickering and Kissin (1936), however, noted no important

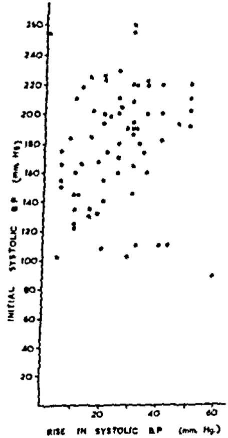



Fig XI 6a

The rise in systolic blood pressure in response to the intravenous injection of 5 units of angiotonin in 50 hypertensive subjects (solid circles) and 20 normotensive subjects (open circles) (Doyle, A. E., and Black, H., Circulation, 12 974-980, 1955, by permission)

difference in the reactions of hypertensives and normotensives of the same age groups; but they commented on the larger responses of old as compared with young age groups. The blood pressure raising reflex from ischaemic muscle is usually greater in hypertensives than in normotensives (Alam and Smirk, 1938).

While a high reactivity is more common in essential hypertension

reactivity of the capillaries of the nailfold in essential hypertension patients than in normal controls.

Black and Doyle (1953) and Doyle and Black (1955) found that the blood pressure rises following equal injections of angiotonin, noradrenaline and S-methyl *iso*-thiourea were slightly greater in essential hypertension than in health but that, following ganglionic blockade

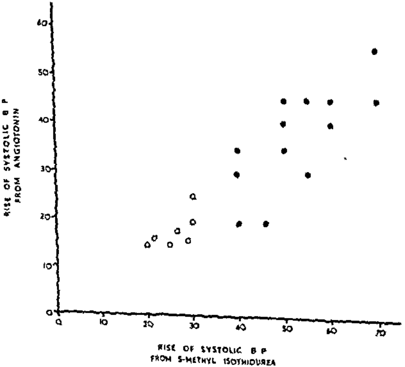



Fig XI 8

with hexameth

reflexes are ... indicates

ty to p

normc

increa ... pressor response of rabbits to ... described a similar ganglionic blockade with hexamethonium.

It is of great interest that patients and normals who show a high degree of reactivity to angiotonin usually show a correspondingly

stimuli (Chapter VII) and the rise of blood pressure on procaine blockade of the carotid sinuses in man (Kezdi, 1953) are all greater, as an average, in essential hypertension than in health. *Barath (1928)*, Eppinger and Kisch (1923), Eppinger and Schwarz (1927), Bauer and

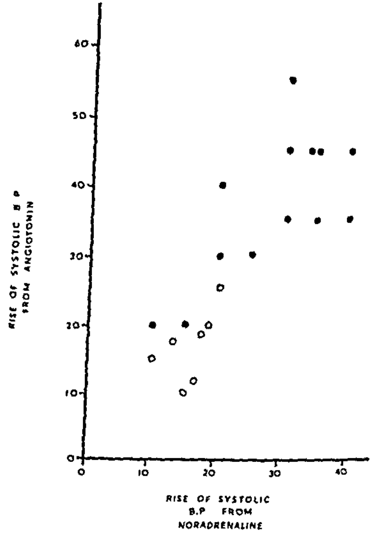



Fig XI 7

Comparison of
in 13 hypertensi
after ganglionic
culation, 12 974-980, 1955, by permission)

Neuburger (1932) and Raab (1954) found that the performance of controlled muscular work raises the blood pressure to a greater degree in essential hypertension than in health, and there have been recent confirmations of this (Chapter IV). Greisman (1954) noted a greater

reactivity of the capillaries of the nailfold in essential hypertension patients than in normal controls.

Black and Doyle (1953) and Doyle and Black (1955) found that the blood pressure rises following equal injections of angiotonin, noradrenaline and S-methyl *iso*-thiourea were slightly greater in essential hypertension than in health but that, following ganglionic blockade

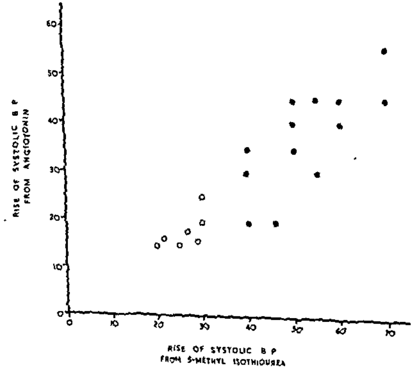



Fig. XI 9

... by permission). ... and

with hexameth...

... are restrained by ganglionic blockade ... that, when homeostatic ... ty to pressor stimul... a much great...

normotension

increase in th...

ganglionic blockade with hexamethonium. ... to noradrenaline after

It is of great interest that patients and normals who show a high degree of reactivity to angiotonin usually show a correspondingly

high reactivity to noradrenaline (Fig. XI 7) and to a synthetic pressor agent S-methyl *iso*-thiourea (Fig. XI 8). This suggests that blood vessels exhibiting a high degree of reactivity to one form of stimulation may also exhibit high reactivity to other stimuli.

It is possible that the differences in the responses of hypertensives and normotensives to nervous stimulation, as by the cold pressor test, would also be more pronounced, were it possible to restrain homeostasis without at the same time interfering with the pathways of pressor reflexes.

One may conclude, from the evidence cited above and in other Chapters, that the blood pressure raising actions of ordinary daily activities, mental, physical and emotional, have usually a much greater effect upon the blood pressures of patients with essential hypertension than upon the blood pressures of normal subjects. In many hypertensives these strong and frequent blood pressure elevations must be responsible for an important part of the elevations of the casual blood pressure upon which a diagnosis, even a prognosis, of hypertension is sometimes based. There is, however, good evidence that these temporary elevations of the supplemental blood pressure are less harmful than elevations of the basal blood pressure.

The question of whether abnormally strong and frequent blood pressure variations may lead sometimes to the development of permanent hypertension remains unsettled.

### Other Self-Perpetuating Mechanisms

Pickering in 1945 discovered that if hypertension induced by renal artery constriction in the rabbit were maintained for two months, nephrectomy did not abolish the hypertension. This showed that hypertension could persist after removal of the original cause (see Chapter IX). It is not known whether such a mechanism operates in man. The persistence of some hypertension after successful surgical treatment of aortic coarctation (Counihan, 1956), is a possible example.

The concept that hypertension may lead to pathological or functional changes which cause further increases of pressure is important, not only for the better understanding of the way in which hypertension develops, but because it is now practicable to control blood pressure levels and it should be possible to interrupt the vicious circle.

## EVIDENCE THAT THE HOMEOSTATIC CONTROL CENTRES REMAIN ACTIVE AND OPERATE AT A HIGHER LEVEL IN ESSENTIAL HYPERTENSION

### Homeostatic Regulation of the Blood Pressure in Essential Hypertension

There is ample evidence that homeostatic regulatory mechanisms retain their activity in essential hypertension, and that they operate

at a higher level. The use of hexamethonium as a means of blockading nerve impulses has provided a wonderful opportunity to study the operations of the homeostatic mechanisms in man. Results relevant to this section are set out in some detail in Chapter XVIII, where the effects of hexamethonium on circulatory homeostasis are described.

The following pattern emerges: in hypertension, as in health, procedures which of themselves would tend to reduce the blood pressure are opposed by the homeostatic mechanisms, which react by increasing the neurogenically maintained fraction of the blood pressure.* The impulses sent out by the nervous system may increase the tone of arterioles and/or veins and venules, and may increase the activity of the heart In contrast, almost all procedures which would tend of themselves to elevate the blood pressure, are opposed by the action of the homeostatic mechanisms. This is done by decreasing the neurogeni-

[illegible]

[illegible]hexamethonium, by blockading ganglia, will induce large falls of blood pressure; when, however, less of the blood pressure is attributable to the neurogenically maintained fraction, then hexamethonium has a diminished effect. Thus, we find that all of the following procedures, which do not ordinarily lower the blood pressure appreciably, because of the action of the homeostatic mechanisms (increasing the neurogenically maintained fraction), have the effect of increasing the blood pressure fall induced by hexamethonium:

1. The standing posture.
2. The application of moderate suction to the external body surface.
3. Venesection.
4. Venous congestion of both lower limbs.
5. Severe salt restriction (due to decrease in blood volume).
6. Resting after muscular exercise (due to vasodilatation [illegible]
7. Meals [illegible]
8. [illegible]
9. Rise in body temperature
10. A hot external environment.

When, however, the homeostatic controls are regulating against procedures tending to raise the blood pressure and the neurogenically maintained fraction of the blood pressure is decreased, the blood pressure fall on administering hexamethonium is much reduced. Thus, we see that it is decreased:

1. After injections of angiotonin, noradrenaline, and S-methyl iso-thiourea

* See definition and explanation, page 327.

2. By the application of positive pressure to the external surface of the body below neck level, either in a pressure chamber or by immersion in water.
3. By infusions of blood or dextran solution.
4. By a cold external environment.

It would be difficult indeed to explain this pattern of response except in terms of the hypothesis that the various procedures described have the tendency either to lower or to raise the blood pressure, but that moves in either direction are normally antagonized and concealed by the action of the homeostatic controls, which withdraw or add neurogenic stimuli to blood vessels, and sometimes to the heart, in such a way that a higher or a lower proportion of the blood pressure is maintained as the result of the discharge of these impulses. All the evidence goes to show that in essential hypertension the vasomotor centres are preserving a high blood pressure level, in that they not only antagonize further rises in blood pressure, but they antagonize stimuli tending to cause falls of blood pressure.

It is not certain whether the action of the vasomotor centres in preserving a high blood pressure is the result of an intrinsic change in the centres or whether it is due to an alteration of the stimuli reaching the vasomotor centres as, for example, from baroceptors.

Other evidence which suggests that in hypertension the blood pressure regulation operates at a higher level is that hypertension is not accompanied ordinarily by any important change in the pulse rate or cardiac output. In general it is to be expected that, when the blood pressure control centres are regulating against the elevated blood pressure, the heart will be slowed

## Activity of the Carotid Sinus Baroceptors in Essential Hypertension

The effects of digital pressure on the carotid sinuses provides good evidence that these baroceptors maintain a degree of activity in patients with hypertension of various kinds. The relative magnitudes, in health and in hypertension, of the blood pressure falls brought about by carotid sinus stimulation have not been settled. When, however, the inhibitory action of the baroceptors is blocked by injection of procaine into each carotid sinus region in man, then it is found that the blood pressure rises considerably (Kezdi, 1953). This indicates that the blood pressure in essential hypertension would be higher but for the continued inhibition of the regulatory centres by the carotid sinus mechanism. This tonic inhibitory action is present also in health.

Volhard (1949) and Kezdi (1953) suggested that rigidity of the walls of the carotid sinuses may cause a decrease in the normal inhibitory function of these baroceptors; hence a rise in blood pressure. In other words, the centre is thought to alter its activity in response to loss of

inhibitory stimuli which it received normally from the baroceptors. In favour of this view is the evidence that the inhibitory effect of the carotid sinuses upon nervous regulatory centres is brought into action, particularly, by the stretching of the walls of the sinuses. With age

hypertensives than in normotensives. It is suggested, therefore, that because of rigidity of the sinus wall, the regulators are unable to prevent rises of blood pressure in the normal way.

There are a few objections to this hypothesis in respect of its application to essential hypertension. In experimental carotid sinus hypertension the pulse rate is considerably increased, but this is not usual in essential hypertension. In almost all cases of carotid sinus hypertension the blood pressure fluctuates and in essential hypertension it is labile in only a proportion of cases. Were rigidity of the carotid sinus the *only* factor responsible for the rise of blood pressure, then it would be expected that complete local anaesthesia of the carotid sinuses would produce rises of the blood pressure to the same height in health and hypertension, and according to Kezdi (1953), it produces a rise to a greater height in hypertension. Another consideration is that rigidity of the carotid sinus will be ...

... of stimulation to which the carotid sinus baroceptors are subjected. As mentioned in Chapter VIII, there is evidence that a pulsating pressure provides a more effective stimulus to the carotid sinus than a non-pulsating pressure, even when the mean pressure is the same. Rigidity in other major vessels might, therefore, neutralize to some extent the effects of rigidity of the sinuses.

The hypothesis that the carotid sinus baroceptors fail to restrain blood pressure rises as well ...
supported by the observ...
that in hypert...
... enaline
... gang-
... homeostasis an-
... the blood pressure rise to a greater extent in the normal, the impairment of homeostasis by hexamethonium should have led to a greater increase of the pressor response ...
the ...

Kezdi ...

... and interruption

of the tracts in the medulla may be the cause of hypertension in bulbar polyneuritis. He does not suggest that rigidity of the carotid sinus walls explains all the blood pressure elevation in essential hypertension.

An interesting observation, which may be indicative of some alteration of the blood pressure regulators, was made by MacWilliam (1925) who noted that Marey's reflex (slowing of the pulse with elevation of the blood pressure) does not operate in high blood pressure as ordinarily encountered. In this connection Alam and Smirk (1938) noted that, whereas reflex blood pressure rises from cold and their blood pressure reflex from muscles, were accompanied in normals by slowing of the pulse, no slowing occurred in hypertensives

## EVIDENCE THAT THE BLOOD PRESSURE ELEVATION IN ESSENTIAL HYPERTENSION IS PARTLY "NEUROGENICALLY MAINTAINED" AND PARTLY IS "NOT-NEUROGENICALLY MAINTAINED"

Consideration of the part played by the nervous system in maintaining the blood pressure elevation in essential hypertension has been left to the end of the chapter, because the subdivision into neurogenically and not-neurogenically maintained hypertension transects all other classifications; for example, it is not unlikely that the nervous system becomes concerned in the later stages of hypertension due to renal ischaemia.

It has been mentioned already that the casual blood pressure may be subdivided into basal and supplemental components. There is good evidence that states of emotion or tenseness raise the level of the supplemental blood pressure in man (Chapters IV and VII). If, therefore, we recognize rises in the supplemental blood pressure as a part of the blood pressure elevation in essential hypertension, then it must be conceded that an important part of the supplemental blood pressure elevation is dependent upon the state of activity of the central nervous system. This statement, however, does not necessarily imply an increase in nervous stimulation above the normal. An alternative explanation is that the amount of nervous stimulation may be within normal limits, the brisk responses to emotional stimuli being due to increased reactivity of the blood vessels.

The difficulty in distinguishing between increase in the stimulus and increase in sensitivity to the stimulus may be circumvented by employing the term "neurogenically maintained" elevation of the blood pressure. Elevations of the blood pressure, associated with an increase of tenseness or emotion are to be regarded as "neurogenically maintained" in the sense that, whether they be due to increased activity of the nervous system above the normal or to enhanced reactivity of the blood vessels, the rises of pressure have been determined by the action of nervous impulses.

So far as the development of clinical manifestations is concerned,

elevations of the basal blood pressure are overwhelmingly more important than elevations of the supplemental blood pressure. The basal blood pressure is very close to the blood pressure during quiet [illegible] probably unrelated to short-term changes in mental or [illegible] blood pressure is [illegible] inistration of [illegible] posture, causes large doses of hexamethonium, even [illegible] substantial falls in the blood pressure to well below the basal level.

## "Floor" Blood Pressures in Essential Hypertension

The extent to which the casual blood pressure falls, after maximal

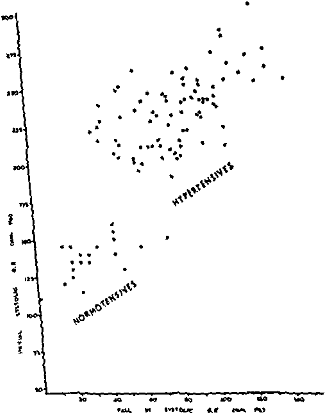



Fig. XI 9

[illegible]

doses of hexamethonium administered intravenously to patients with essential hypertension, varies considerably from case to case. As far as is known, the hypotensive action of hexamethonium is due solely to

the effects of the drug upon the nervous system, namely, blockade of sympathetic and parasympathetic nerve ganglia, perhaps assisted by some central sympathetic inhibition (Dontas and Nickerson, 1955). It would seem, therefore, that the extent to which the blood pressure is "neurogenically maintained" also varies from case to case. The "neurogenically maintained" fraction of the casual pressure is composed of part of the basal and much of the supplemental blood pressure.

In the majority of patients, following maximal doses of hexamethonium, the "floor" blood pressure is appreciably above the "floor"

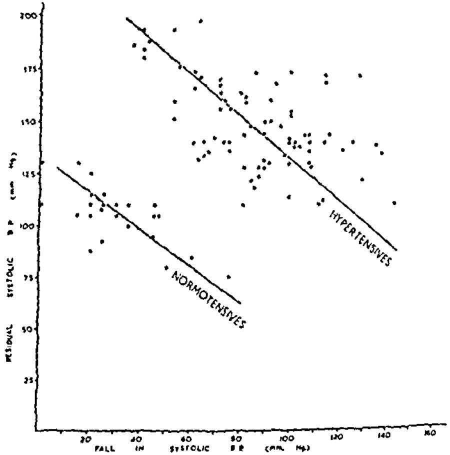



Fig. XI 10

The relation between the "floor" or "residual" blood pressure after administration of ... the blood ... and in ... blood ... 55, by ... mission)

blood pressure of normotensives. Hence, it may be inferred that in essential hypertension there is also an increase in the "not-neurogenically maintained" fraction. Smirk and Doyle (1954) and Doyle and Smirk (1955) made observations in 80 patients with hypertension of

various types with a mean blood pressure for the group of 233/133 mm. Hg. The mean fall in the blood pressure in the horizontal posture, following hexamethonium bromide, was 85/38 mm. Hg. The average level of the "floor" blood pressure after hexamethonium varied considerably but the mean level was 148/95 mm. Hg. In the normotensive controls the mean casual blood pressure was 137/82 and the "floor" blood pressure was 106/67. Thus, when we compare our essential hypertension patients with our normal controls we find:

| | Essential hypertension | Normal | Difference |
|---|---|---|---|
| Casual Blood pressure . . . . . | 233/133 | 137/82 | 96/51 |
| Floor Blood pressure . . . . . (not-neurogenically maintained fraction) | 148/95 | 106/67 | 42/28 |
| Fall in blood pressure with hexamethonium . . . . (neurogenically maintained fraction) | 85/38 | 31/15 | 54/23 |

Therefore, in essential hypertension there are increases in the neurogenically and in the not-neurogenically *maintained* fractions of the blood pressure. The average degree *of increase* is about the same in the two fractions but the *proportions differ greatly from* one patient to another

*Results very similar* to ours were obtained by Barnett and Fraser (1954) who found *the blood pressure falls* were greater in essential hypertension than *in health*.

A point of some interest is that in *normotensives* and in hypertensives the falls of blood pressure after hexamethonium increase as the [illegible] The relationship between [illegible] (or floor) blood pressure is [illegible] high floor blood pressures are associated with low falls of blood pressure and *vice versa* (Fig. XI 10).

## Relation of Cardiac Output to "Floor" Blood Pressure

The fall of blood pressure after hexamethonium might be due to decrease in the peripheral resistance or to decrease in the cardiac output or to some combination of these.

It has been [illegible] after hex[illegible] resistance [illegible] McMichae[illegible] [illegible] Royel, Huggins, Handley and Mills, 1952; Rakita

the effects of the drug upon the nervous system, namely, blockade of sympathetic and parasympathetic nerve ganglia, perhaps assisted by some central sympathetic inhibition (Dontas and Nickerson, 1955). It would seem, therefore, that the extent to which the blood pressure is "neurogenically maintained" also varies from case to case. The "neurogenically maintained" fraction of the casual pressure is composed of part of the basal and much of the supplemental blood pressure.

In the majority of patients, following maximal doses of hexamethonium, the "floor" blood pressure is appreciably above the "floor"

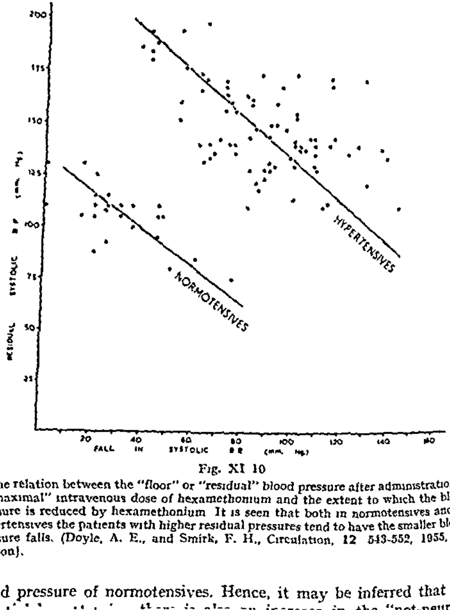



Fig. XI 10

The relation between the "floor" or "residual" blood pressure after administration of a "maximal" intravenous dose of hexamethonium and the extent to which the blood pressure is reduced by hexamethonium It is seen that both in normotensives and in hypertensives the patients with higher residual pressures tend to have the smaller blood pressure falls. (Doyle, A. E., and Smirk, F. H., Circulation, 12 543-552, 1955, by mission).

blood pressure of normotensives. Hence, it may be inferred that in [illegible] e in the "not-neuro- [illegible] (1954) and Doyle and [illegible] with hypertension of

bromide caused much smaller falls in the blood pressure (Figs. XI 11 and 12). This happens whether the patient is in the horizontal or in the vertical posture. The following suggestion is offered, *namely*, that when humoral substances are administered, either in normotensives or

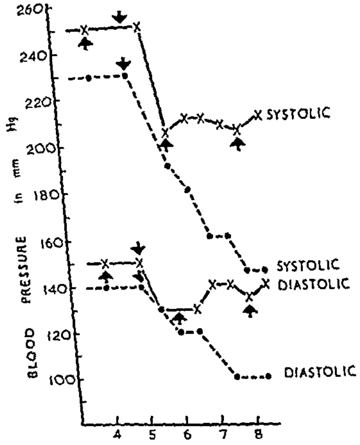



*Fig* XI 11

The effect of experimental elevation of the blood pressure by a humoral agent upon the fall of blood pressure from the subsequent administration of hexamethonium. Blood pressure falls (horizontal posture) in a hypertensive patient following a large intravenous injection of hexamethonium ↓• — — — — — • under control cond[illegible] X — — — — — X during blood pressure elev[illegible] intervals of [illegible]

in hypertensives, their tendency to elevate the blood pressure is antagonized by the normal regulatory mechanisms which operate by causing a decrease in the amount of neurogenic tone. In other words, when the humorally maintained fraction of the blood pressure is

and Sancetta, 1953). Other authors found a decrease in the cardiac output (Werkö et al., 1951; Freis et al., 195[illegible] [illegible] law it w[illegible] and hyp[illegible] the hype[illegible].

As hexamethonium given to patients at rest causes some fall in the venous pressure, it is not unlikely that, in some instances at least, a fall in the cardiac output occurs, which is probably due to an effect of hexamethonium on the venous side of the circulation.

It has been pointed out by Gollwitzer and Meier (1929), Fleisch (1930) and Landis and Hortenstine (1950) that changes in the calibre of the arterioles and the veins are nearly always in the same direction, as for example when sympathetic tone is increased or diminished. It seems very probable, therefore, that under ordinary circumstances, hexamethonium causes not only a decrease in the calibre of the arterioles, but also a decrease in the tone of the veins; and the decrease in the "neurogenically maintained" fraction of the blood pressure in hypertension is due to these two peripheral vascular actions, both of which are the result of sympathetic blockade.

The falls of blood pressure in spinal anaesthesia are also greater in essential and advanced renal hypertension than in health (Gregory and Levin, 1945), and no doubt decrease in venous tone plays some part (Smith et al., 1939) as well as decrease of peripheral resistance.

Fundamentally the action of the hexamethonium is to disturb the relationship between cardiac output and peripheral resistance, in other words, to interfere with the operation of the mechanism responsible for regulation of the blood pressure level. When the nervous regulating centres are in full activity, and are not handicapped either centrally or by ganglionic blockade, a moderate decrease in the cardiac output leads to peripheral constriction involving arterioles and veins and the blood pressure level is maintained.

## Effect of Increasing the Not-Neurogenically Maintained Part of the Blood Pressure in Man

In essential hypertension a peripheral resistance is maintained which is high relative to the cardiac output. Neither the peripheral resistance nor the cardiac output is static but, under many of the physiological conditions which cause them to vary, the central nervous regulation continues to operate so as to maintain the abnormal relationship.

It becomes of interest to know in what way the presence in the circulating blood of pressor substances would influence the operation of the central nervous regulation. Smirk and Doyle (1954) and Doyle and Smirk (1955) found that following the administration of angiotonin, S-methyl *iso*-thiourea or noradrenaline, in doses sufficient to raise the blood pressure, the subsequent administration of hexamethonium

fraction of the blood pressure by hexamethonium will produce a bigger fall of blood pressure if the blood pressure is already high, from the presence of a humoral substance, than if the blood pressure starts out at a lower level. Our observations are inconsistent with this hypothesis. In both normotensives and hypertensives the reactions to hexamethonium which we have observed, after the blood pressure has been raised by representative pressor agents, differ strikingly from the reactions observed in patients with unmodified essential hypertension. It is suggested that while the regulatory centres are acting there will be a reciprocal relationship between the humoral and nervous tone. If there is a fall in the non-neurogenic fraction of the blood pressure, neurogenic tone will be increased, whereas if the non-neurogenic tone is increased there will be a compensatory decrease in the neurogenic tone.

### Evidence Compatible with the Occurrence of an Acute Form of Humoral Hypertension in Man - Its Possible Relationship to Chronic Humoral Hypertension and the Theories of Wollheim and Grollman

It is of interest that there are a few patients who become almost completely resistant to methonium salts and fail to get blood pressure falls either in the horizontal or in the sitting posture (McQueen and Smirk, 1955). Almost all of these patients, about six in number out of approximately 500 who have received methonium salts here, in the course of treatment or clinical trials, have either been examples of renal disease or have recently suffered a *cerebral haemorrhage* involving brain substance Most of the patients referred to had been under [illegible]

[illegible] act through the nervous system. In one patient we obtained falls of blood pressure with hydralazine. Dr. Charles Burns, of Wellington, kindly supplied me with details of a boy aged 4, with casual blood pressures in the region of 230/200 with an aneurysm of a renal artery (Fig. VI 1). Very large doses of hexamethonium injected intravenously, caused no fall of blood pressure. Our impression is that such cases are probably examples of acute humoral hypertension Perhaps the insensitivity to hexamethonium is similar to the irresponsiveness of patients who have been given intravenous injections of pressor substances, such as [illegible]

In [illegible]
be [illegible]
lar [illegible] interest in that very [illegible] pressure in the horizontal posture may be obtained

increased, the "neurogenically maintained" fraction is decreased by the action of the homeostatic controls; hence, as there is then less neurogenic tone to remove, the fall of blood pressure from hexamethonium is diminished.

These results are of interest in relation to a suggestion which is often

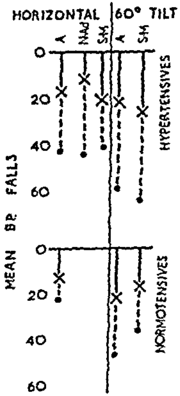



Fig XI 12

*The lengths of the lines down to the dots represent the falls of blood pressure from large intravenous doses of hexamethonium The lengths of the lines down to the crosses represent the smaller falls of blood pressure from the same doses of hexamethonium when the blood pressure has been first raised to a higher level by intravenous injection of a pressor agent. Each line represents the mean of 10 to 12 experiments. The results obtained with angiotonin are marked "A", with noradrenaline "N-Ad", with S-methyl iso-thiourea "SM". "Horizontal" and "60 degree tilt" refer to the positions of the patients during the investigation. Results on hypertensives and normotensives are set out separately. (Doyle, A. E, and Smirk, F H, Circulation, 12 543-552, 1955, by permission)*

made to explain the high reactivity of the blood pressure in essential hypertension to nervous stimuli; and to explain the large blood pressure falls which occur if nervous control over blood vessels is inhibited. It has been suggested that when the blood pressure is raised by a humoral agent, the subsequent administration of a nervous stimulus will give rise to a larger blood pressure increase because the blood vessels are already contracted, so that a small additional change may be expected to have a large effect on the peripheral resistance. Likewise, it has been supposed that removal of the normal "neurogenically maintained"

discussed.

When the sympathetic control over the blood vessels of a limb is removed there is an increase in blood flow — more particularly in skin. Prinzmetal and Wilson (1936) and Pickering (1936) compared the resulting increase in blood flow in hypertensives and normotensives and drew conclusions from results concerning the nature of the increase of peripheral vascular tone in hypertensives. Recently, Pickering (1955) has pointed out that there are technical objections to the original procedure in which the hand and forearm circulations were studied together. Nevertheless, the method led on to other similar studies in which this source of error was avoided [14, 41, 47]. The results of experiments of this type have been used by some authors as an important argument against the participation of neurogenic factors in the pathogenesis of hypertension [41, 61, 64] Under average conditions the peripheral blood flow is often about the same in patients with essential

... peripheral resistance is

... pathetic nervous control

... heating or by blockade of nerves, the peripheral blood flow increases in normotension and in hypertension, but Prinzmetal and Wilson found that the increase was no greater in hypertension. From this it was argued that normal sympathetic activity is present in essential hypertension but that there is no *increase* of sympathetic tone; in other words the increase of peri-

... There seems, however, to be

... ults.

... above have been discussed largely in terms of alternatives, *namely*, that the increased peripheral resistance was due either to an increase in neurogenic tone or, alternatively, that it was due to increased peripheral resistance of some other kind, which was not neurogenic. In terms of unitarian hypotheses, the conclusion that the increase *in tone* is not neurogenic would seem to be a valid inference.

If we assume that both neurogenic and non-neurogenic increases of peripheral resistance may be concerned, then there are algebraic reasons for preferring the inference that, when the arm blood flows of normotensives and hypertensives are similar, both before and after inhibition of sympathetic control over blood vessels, the neurogenic and non-neurogenic tone are both increased and to a corresponding degree.

in malignant hypertension patients by the administration of large doses of hexamethonium. This indicates that if angiotonin is in part responsible for the blood pressure rise there must be also a considerable rise in the "neurogenically maintained" fraction.

My interpretation of the evidence derived from injecting angiotonin and other pressor agents into hypertensives is that the results are not incompatible with the occurrence in essential hypertension of a circulating pressor agent (e.g., angiotonin or even pherentasin (Schroeder, 1953)) provided one assumes that the level of operation of the homeostatic controls has been lifted.

The capacity to buffer blood pressure rises depends on the control centres having available a neurogenically maintained fraction of the blood pressure which can be inhibited in response to pressor stimuli. The presence of this neurogenically maintained fraction is detected by administration of hexamethonium. If we assume that in chronic humoral hypertension the centres have become adjusted to a higher level, by increasing the neurogenically maintained fraction, then they will once more be able to react to further increases in the amount of the pressor agent by decreasing the neurogenically maintained fraction of the blood pressure.

The same reasoning can be applied to hypotheses which explain hypertension in terms of loss of depressor principles.

Wollheim (1936, 1937, 1945) considers that a non-dialysable thermostable substance "depressan", which he is able to obtain from human and animal urine, is concerned in the pathogenesis of essential hypertension. The substance causes blood pressure falls. Grollman (1953) accepts essential hypertension as having a renal origin and refers to the possibility that the kidney, in addition to its excretory function, maintains some metabolic activity or produces some incretory product, the absence of which from the organism results in the manifestation of hypertensive disease. The many observations made in recent years on renoprival hypertension support the view that some such factors are likely to be concerned, at least as partial explanations of experimental renal hypertension in animals. It would be interesting to know if there is some relationship between Wollheim's lack of "depressan" theory and Grollman's concept of renal incretory function. The absence of a normal vasodilator (substance or incretory influence) should also induce a rise in the level of operation of the homeostatic controls.

## Nervous and Non-Nervous Control of the Blood Vessels in Hypertension as Studied on the Circulation of Limbs.

Studies of the arm or hand circulation have led many observers to conclude that, in essential hypertension, the increase in peripheral resistance is not neurogenic. There is, however, ample evidence, from

may influence blood pressure by its effect on salt metabolism. As McQueen and Veale (1955) have shown, loss of the adrenal glands also decreases the reactivity of perfused rat blood vessels to certain pressor stimuli.

The relationship of the adrenal glands to hypertension is discussed further in Chapters VI and IX and a valuable review has been publisbed by Perera (1950). My impression is that the adrenal cortex is necessary for the efficient working of the circulatory system; hence, when there is a deficiency of the adrenal cortex hormones, it is more difficult to sustain high levels of the blood pressure. There is not much evidence that increase of the adrenal cortex hormones we know of, even of the recently discovered aldosterone, has a dominant role in the pathogenesis of essential hypertension. There is some evidence, however, of increased excretion of aldosterone in hypertension (see Chapter VI), and Hajdu and Leonhard (1956) have used change in the Bowditch staircase phenomenon in the frog's heart for bioassay of corticoid like activity in human plasma, and find an increase in essential hypertension.

## Salt Metabolism

Excess of salt increases, and severe deprivation decreases, the level of the blood pressure both experimentally and clinically (Chapters IX and XV). Teng et al (1954) consider that there is an appreciable expansion of extracellular volume, and it is recognized that there are some departures from the normal in the metabolism of water and salt in patients with essential hypertension. Whether these changes are related to some basic disturbance concerned in pathogenesis or whether some of them are the result of altered exchange in capillaries due to the hypertension is unsettled. Tobian and Binion (1952) think that water retention might thicken the walls of arterioles and be responsible for increased peripheral resistance. Ross (1956) has estimated the total exchangeable sodium in hypertensive and normotensive subjects using $^{24}$Na. In some hypertensive subjects the exchangeable sodium was within the normal range, in others it was well above the normal range. In the patients with an excess of exchangeable sodium, determinations of the plasma sodium and the extracellular fluid volume suggested that the excess sodium was not located in the extracellular but in the intracellular compartment. In the normal group the mean "intracellular" sodium was considered to be $43.0 \pm 2.1$ m Eq./l, in those of the hypertensive group who exhibited a high total exchangeable sodium the intracellular sodium was $93.8 \pm 6.0$, which is well outside the normal range of 32—54 m.Eq /l. These are large differences, but the reason why the exchangeable sodium [illegible]

*Effect of proportional increase of neurogenic and non-neurogenic peripheral resistance.* — If $x$ per cent of the peripheral resistance of a region is neurogenically maintained both in normotension and in hypertension, then, if the blood pressures are unchanged, removal of the neurogenic fraction will decrease the peripheral resistance by $x$ per cent in each case and therefore will multiply the flow by $\left(\frac{100}{100 - x}\right)$. If the blood flows are the same before removal of the neurogenic fraction then, in this example, they will increase to the same degree and attain the same level after sympathetic inhibition. But if $x$ per cent of the peripheral resistance is neurogenic in normotension and essential hypertension, it follows that as the peripheral resistance is greater in hypertension, so also is the neurogenic component.

A general rule relating to blood flow through organs can be derived, namely, that when in hypertension (as compared with normotension) there is proportionately a greater increase in the neurogenic fraction of the peripheral resistance, then, when the neurogenic fraction of the peripheral resistance is removed by sympathetic inhibition, there will be a greater increase in the blood flow to the part (in hypertension than in normotension). In contrast, if in hypertension (as compared with normotension) there is proportionately a greater increase in the non-neurogenic fraction, then there will be a smaller increase of the blood flow in hypertension (as compared with normotension), when the neurogenic fraction of the peripheral resistance is removed.

The general impression is that the neurogenically and not neurogenically maintained fractions of the blood pressure are both increased in essential hypertension. Their relative magnitudes vary from case to case.

Recent observations by Mendlowitz (1951) and Caliva et al. (1954), on blood flows before and after blockade of nerves, suggest that an important part of the increase in the peripheral resistance in fingers and toes is neurogenic in cases of essential hypertension without renal function defects. Caliva et al. (1954) found an increase in non-neurogenic peripheral resistance in the blood vessels of toes, in patients with nitrogen retention and marked retinopathy

## OTHER FACTORS WHICH MAY BE CONCERNED

### Adrenal Cortex Hormones

Experimental and clinical evidence makes it clear that the level of the blood pressure is related to the status of the adrenal cortex, in that it is more difficult to maintain hypertension when there is a deficiency of adrenal cortical hormones and perhaps easier to maintain high levels when the cortical hormones are in excess. The adrenal cortex

may influence blood pressure by its effect on salt metabolism. As McQueen and Veale (1955) have shown, loss of the adrenal glands also decreases the reactivity of perfused rat blood vessels to certain pressor stimuli.

The relationship of the adrenal glands to hypertension is discussed further in Chapters VI and IX and a valuable review has been published by Perera (1950). My impression is that the adrenal cortex is necessary for the efficient working of the circulatory system; hence,

[illegible]

even of the recently discovered aldosterone, has a dominant role in the pathogenesis of essential hypertension. There is some evidence, however, of increased excretion of aldosterone in hypertension (see Chapter VI), and Hajdu and Leonhard (1956) have used change in the Bowditch staircase phenomenon in the frog's heart for bioassay of corticoid like activity in human plasma, and find an increase in essential hypertension.

## Salt Metabolism

[illegible]

of [illegible]

an [illegible] (1954) consider that there is an appreciable [illegible]

[illegible] essential hypertension. Whether these changes are related to some basic disturbance concerned in pathogenesis or whether some of them are the result of altered exchange in capillaries due to the hypertension [illegible]

[illegible] Ross (1956) has estimated the total exchangeable sodium [illegible]
$^{24}$Na. In [illegible]
within th[illegible]
In the [illegible]

[illegible] group the mean "intracellular" sodium was considered to be 43 0±2.1 m.Eq./l; in those of the hypertensive group who exhibited a high total exchangeable sodium the intracellular sodium was 93.8±6 0, which is well outside the normal range of 32—54 m Eq./l These are large differences, but the reason why the exchangeable sodium remains [illegible]

*Effect of proportional increase of neurogenic and non-neurogenic peripheral resistance.* — If $x$ per cent of the peripheral resistance of a region is neurogenically maintained both in normotension and in hypertension, then, if the blood pressures are unchanged, removal of the neurogenic fraction will decrease the peripheral resistance by $x$ per cent in each case and therefore will multiply the flow by $\left(\frac{100}{100-x}\right)$. If the blood flows are the same before removal of the neurogenic fraction then, in this example, they will increase to the same degree and attain the same level after sympathetic inhibition. But if $x$ per cent of the peripheral resistance is neurogenic in normotension and essential hypertension, it follows that as the peripheral resistance is greater in hypertension, so also is the neurogenic component.

A general rule relating to blood flow through organs can be derived, namely, that when in hypertension (as compared with normotension) there is proportionately a greater increase in the neurogenic fraction of the peripheral resistance, then, when the neurogenic fraction of the peripheral resistance is removed by sympathetic inhibition, there will be a greater increase in the blood flow to the part (in hypertension than in normotension). In contrast, if in hypertension (as compared with normotension) there is proportionately a greater increase in the non-neurogenic fraction, then there will be a smaller increase of the blood flow in hypertension (as compared with normotension), when the neurogenic fraction of the peripheral resistance is removed.

The general impression is that the neurogenically and not neurogenically maintained fractions of the blood pressure are both increased in essential hypertension Their relative magnitudes vary from case to case.

Recent observations by Mendlowitz (1951) and Caliva et al. (1954), on blood flows before and after blockade of nerves, suggest that an important part of the increase in the peripheral resistance in fingers and toes is neurogenic in cases of essential hypertension without renal function defects. Caliva et al. (1954) found an increase in non-neurogenic peripheral resistance in the blood vessels of toes, in patients with nitrogen retention and marked retinopathy

## OTHER FACTORS WHICH MAY BE CONCERNED

### Adrenal Cortex Hormones

Experimental and clinical evidence makes it clear that the level of the blood pressure is related to the status of the adrenal cortex, in that it is more difficult to maintain hypertension when there is a deficiency of adrenal cortical hormones and perhaps easier to maintain high levels when the cortical hormones are in excess. The adrenal cortex

to the subsequent development of essential hypertension include: certain environments, certain dietary habits, race, heredity, emotional lability or disposition to over-alertness and tenseness, occupations or domestic environments involving a tendency to stress and strain, over-average liability of the vasomotor system to respond by vasoconstriction to tenseness and emotion, physical activity or metabolic stimuli, overaverage body weight or sthenic habitus. In some instances observations have been made concerning the effects of these factors on the supplemental and basal pressures.

6. If elevation of the blood pressure in essential hypertension depends, at some stages, upon the total effect produced by the combined action of several components, it becomes important to know whether the magnitude of the total effect is equal to the sum of the effects of the various components acting separately. The answer appears to be that, in some cases at least, the blood pressure rise produced by two blood pressure raising stimuli acting simultaneously is less than the sum of the blood pressure rises produced by the two stimuli acting separately.

7. By definition casual B.P. = basal B.P. + supplemental B.P. Elevations of the basal blood pressure, being more persistent, throw greater strain on the heart and on small arteries and arterioles than the elevations of the supplemental pressure. We have made basal blood pressures in over 1,000 hypertensives. It is clear that the clinical manifestations secondary to hypertension and the mortality are much more closely correlated with elevation of the basal than with elevation of the casual blood pressure. (Indeed, elevation of the supplemental pressure does not increase either the mortality or the association with manifestations secondary to hypertension).

8. In New Zealand the mean basal and supplemental [illegible] [illegible] increases of blood pressure with age form a part of the blood pres[illegible] and play a part in the develo[illegible] disorder.

9. There is some evidence which is compatible with the idea that the rises of basal and supplemental blood pressure occur independently and that, to a certain extent, rise in the casual blood pressure is a statistical coincidence being the sum of two variables.

10. The stimuli which elevate the supplemental blood pressure in essential hypertension seem to be the same as those which operate in normotension. As an average the supplemental pressures, during exposure to a variety of stimuli, are greater in essential hypertension than in normotension and often within or below the normal range in re[illegible] hypertension.

## SUMMING UP ON PATHOGENESIS

The following is a new edition of a working hypothesis (Smirk, 1946, 1949). It has had the advantage to the author of suggesting a number of investigations and an approach to therapy. An attempt to present the subject as a whole involves including ideas, many of which will certainly need revision. Where the reader turns to other parts of the book referred to in this chapter he will find an attempt to evaluate the evidence for statements made. These are scattered throughout the book, as it was difficult to assemble them all under the heading of pathogenesis without dispersing the subject matter of several topics.

1. It is possible to explain the unity of the clinical picture in essential hypertension by the fact that the clinical manifestations and complications are due, almost entirely, to events which are secondary to a single characteristic of the disorder, namely high blood pressure brought about by vasoconstriction. This explains why the clinical manifestations characteristic of essential hypertension occur in a pure form in that disorder and occur in association with other characteristic clinical manifestations in the various forms of secondary hypertension.

2. The degree to which blood vessels are able to withstand exposure to overaverage blood pressure or vasoconstriction without undergoing pathological change, varies from one individual to another, and is likely to have an important influence both on the rate of increase of the blood pressure and on the development of complications. (For example, females tolerate high blood pressure better than males, and there are also differences among patients of the same sex). It is not to be expected, therefore, that there will be an exact correspondence between blood pressure level (even the basal) and clinical manifestations

3. The suggestion is that essential hypertension first emerges as a recognizable disorder as the blood pressure rises, and that no single or simple antecedent cause explains this rise of blood pressure. Hence the term "essential hypertension" is appropriate. In some instances the disorder may begin with simple overactivity of physiological processes, whereas in others pathological changes such as renal arteriosclerosis may be primary, and the proportions vary.

4. In population surveys of various types underaverage blood pressures are associated with a much decreased incidence of essential hypertension in later life. It is difficult to explain this protective influence of low blood pressure except by the hypothesis that the incidence of high blood pressures in later life is influenced strongly by the precise level of the blood pressure at an earlier age, even when this lies within the usual range.

5. Examples of factors which, in suitable combinations, may raise the level of the blood pressure sufficiently to enhance the liability

same person. On assumption of the sitting or erect postures, the "neurogenically maintained" fraction increases considerably and the "not-neurogenically maintained" fraction is neutralized to an important extent by gravitational distension of dependent vessels.

After venesection, salt deprivation or other procedures tending to decrease blood volume, the "neurogenically maintained" fraction rises to compensate for a decrease in the "not-neurogenically maintained" fraction. In essential hypertension patients in the erect posture these homeostatic regulations maintain a high blood pressure by means of sympathetic control over the calibre of arterioles, veins, and perhaps capillaries In most severe hypertensives the blood pressure can be reduced in the erect posture from, say, 270/160 to 70/50 or less by hexamethonium. In this example, 200/110 mm. Hg or more of the blood pressure is "neurogenically maintained" and 70/50 or less is "not-neurogenically maintained". If a humoral pressor agent is first administered, less nervous control of blood vessels is required, and the fall of blood pressure after hexamethonium is reduced, even in the standing posture. In the horizontal posture the "not-neurogenically maintained" fraction of the blood pressure is rather larger than the "neurogenically maintained" fraction, in both normotensives and hypertensives

19. There is good evidence that in man certain disturbances of the renal circulation (especially those involving main renal arteries) lead to a Goldblatt type of hypertension. In experimental animals, there is evidence that liberation of pressor agents and decrease in the amount of healthy renal tissue are both concerned in the blood pressure elevation.

20 There is little *direct* evidence that disturbances of the renal circulation are responsible for any part of the blood pressure elevation in essential hypertension. There is, however, evidence that the renal circulation is reduced in some patients with essential hypertension. It seems likely that in some patients and in certain stages of essential hypertension, a Goldblatt mechanism is concerned in the blood pressure elevation.

21 There is strong evidence that interference with the renal circulation by arteriosclerosis may be primary or may be [illegible]
or caused by [illegible]
for part [illegible]
hyperten[illegible]
increased. [illegible] blood pressure is further

22 It is suggested that in essential hypertension the initial blood pressure increases may be of varied or of [illegible]
these [illegible]

11. *The part played by psychogenic factors is discussed.*

12. There is ample evidence that in essential and most other forms of hypertension the nervous regulation of the blood pressure continues to operate, but its aim is directed at a higher target. The nervous regulation tends to preserve a certain hypertensive level: stimuli tending to reduce the blood pressure being antagonized as well as those tending to increase it further.

13. The application of various pressor stimuli to the nervous system leads, as an average, to larger blood pressure rises in essential hypertension than in normotension. The blockade of efferent sympathetic pathways by hexamethonium leads to much larger falls of blood pressure in essential hypertension than in normotension. It is often [illegible] responses in essential

[illegible]

system.

14. It is possible, however, to state the extent to which the blood pressure is "neurogenically maintained", in the sense that, when the nerve impulses to heart and blood vessels are interrupted, the blood pressure falls to that extent.*

15. An important part of the basal blood pressure and most of the supplemental pressure is "neurogenically maintained". In essential hypertension there is usually an increase in both the "neurogenically" and the "not-neurogenically maintained" fractions of the blood pressure.*

16. The results of certain experiments on limb circulation which have been c[illegible] [illegible]athetic tone in esse[illegible] conclusion. [illegible] tion in the proportions of nervous and non-nervous peripheral resistance, but, as an average, the increases of nervous and non-nervous components of the peripheral resistance are of the same order. This result is consistent with the results obtained with large doses of hexamethonium.

17. After very large doses of hexamethonium the "floor" blood pressure (horizontal posture) is higher in essential hypertension than in normotension. This and other evidence suggests that, in most essential hypertension patients, there is an increase in the "not-neurogenically maintained" fraction of the blood pressure as well as in the "neurogenically maintained" fraction.

18. It is sometimes assumed that in any individual, normotensive or hypertensive, there is some characteristic relationship between the "neurogenically maintained" and "not-neurogenically maintained" fractions of the blood pressure. This, however, is not the case; there are wide variations from person to person, and at different times in the

* For definitions see page 327.

8 Barnett, A J., and Fraser, J. R. E. The mechanism of arterial hypertension A comparison of the effects of hexamethonium bromide in hypertensive and normotensive persons. Aust Ann. Med., 3: 152, 1954.

9 Bauer, J., and Neuburger, F. Die Blutdruckreaktion auf körperliche Arbeit bei abnormen Blutdruck. Z. klin. Med, 120: 628, 1932.

10 Black, H, and Doyle, A. E. Comparison of the effects of angiotonin and s-methyl *iso*-thiourea in normotensive and hypertensive patients Proc. Univ. Otago med Sch, 31: 4, 1953

11 [illegible]

12 [illegible]

13 Byrom, F B, and Dodson, L. F. The mechanism of the vicious circle in [illegible]

14 [illegible]

15 Conway, J The behaviour of the blood pressure in normal and hypertensive rabbits in response to l-noradrenaline and to ganglion block by hexa or pentamethonium J. Physiol (Lond.), 127: 69, 1955.

16 Corcoran, A C, Page, I H, Masson, G. M. C., Taylor, R D., and Dustan, H Hypertension and hypertensive cardiovascular disease — Review of recent observations Arch intern. Med, 87: 732, 1951.

16a Counihan, T B. Changes in the blood pressure following resection of coarctation of the aortic arch. Clin. Sci, 15: 149, 1956.

17 Crumpton, C W, Rowe, G G, O'Brien, G, and Murphy, Q. R. The effect of hexamethonium bromide upon coronary flow, cardiac work and cardiac efficiency in normotensive and renal hypertensive dogs Circulation Research, 2. 79, 1954

18 Dahl, L K, and Love, R A Evidence for relationship between sodium (chloride) intake and human essential hypertension Arch. intern Med., 94 525, 1954

19 Dontas, A S, and Nickerson, M Central nervous system effects of ganglionic blocking agents J Pharmacol, 113, 16, 1955

20 Doyle, A E, and Black, H Reactivity to pressor agents in hypertension. Circulation (N Y), 12 974, 1955

21 Doyle, A E, and Smirk, F. H The neurogenic component in hypertension Circulation (N.Y), 12 543, 1955

22 Eppinger, and Kisch Die Nephritisfrage Wien, 1923 Cited by Raab, W., Ergebn inn. Med Kinderheilk., 46 452, 1934

23 Eppinger, and Schwarz Das Versagen des Kreislaufes Berlin, 1927. Cited by Raab, W, Ergebn inn Med Kinderheilk, 46. 452, 1934.

24 Fahr, G, Davis, J, Kerkhof, A, Hallock, P, and Gierr, E. Hemodynamics of arteriosclerosis — Influence of change of coefficient of volume elasticity on circulation Amer J. Physiol., 101: 376, 1932.

25 Fishberg, A M Hypertension and nephritis. Lea and Febiger, Philadelphia 1954

26 Fleisch, A Venomotorenzentrum und Venenreflexe. I. Mitteilung. Pflügers Arch ges Physiol., 225: 26, 1930

27 Freis, E D, Rose, J C., Partenope, E A, Higgins, T. F., Kelley, R. T. Schnaper, H. W., and Johnson, R L The hemodynamic effects of hypotensive drugs in man III Hexamethonium J clin. Invest, 32: 1285, 1953

28 Gilmore, H R, Kopelman, H, McMichael, J, and Milne, I. G. The

Examples of pathological and functional changes which, in various combinations, might be responsible for further elevations of the blood pressure include:

(a) alteration in the level at which homeostatic reflexes operate, due to a change in the nervous centres brought about by continued exposure to high blood pressure (or possibly by rigidity of the carotid and aortic walls leading to curtailment of the activity of baroceptors),

(b) by inelasticity of the arterial reservoir causing systolic hypertension,

(c) by release of pressor agents from ischaemic kidneys,

(d) by other effects (of the renoprival type) induced by renal ischaemia, including increased vascular reactivity to pressor stimuli,

(e) by exaggerated contraction of hypertrophied arterioles,

(f) by unknown non-renal factors capable of perpetuating certain blood pressure increases, after the primary exciting causes of these increases have ceased to operate (Pickering, 1945).

23. Alterations of salt metabolism and of the urinary excretion of adrenal cortical hormones may occur in hypertension, but the significance of these changes is at present uncertain.

24. If the above general hypothesis is true, namely that elevations of blood pressure in man and certain other mammals tend to be self-perpetuating, it is to be expected that the cycles of changes concerned in the secondary elevations of the blood pressure which occur in essential hypertension will be responsible *in part* for the perpetuation, and perhaps for the further increase of blood pressure in certain other conditions such as post-toxaemia of pregnancy, cortical hyperadrenia and some cases of chronic pyelonephritis, medullary hyperadrenia, and of chronic nephritis.

## References


1 Alam, M., and Smirk, F. H. Blood pressure raising reflexes in health, essential hypertension, and renal hypertension. Clin Sci, 3. 259, 1938

2 Arnold, O H Akute Infektionskrankheiten und Hochdruck Georg Thieme, Stuttgart, 1949.

3 Arnold, O. H. Neure Gesichtspunkte zur Genese und Systematik der Krankheiten mit arterieller Hypertonie Munch med. Wschr., 94. 2358, 2423, 1952.

4 Asteroth, H., and Kreunziger, H. Dehnungsstudien am isolierten Sinus Caroticus von verstorbenen Normotonikern und Hypertonikern. Z. KreislForsch, 40: 11, 1951.

5 Ayman, D., and Goldshine, A D. Cold as a standard stimulus of blood pressure — A study of normal and hypertensive subjects New Engl. J. Med., 219: 650, 1938.

6 Ayman, D., and Goldshine, A D The breath-holding test — A simple standard stimulus of blood pressure. Arch. intern. Med, 63: 899, 1939.

7 Barath, E. Arterial hypertension and physical work. Arch intern. Med, 42. 297, 1928

48 MOYER, J. H, HUGGINS, R. A, HANDLEY, C. A., and MILLS, L. C. Effect of hexamethonium chloride on cardiovascular and renal hemodynamics and on electrolyte excretion. J. Pharmacol, 106: 157, 1952
49 OEHME, C Übersichten. Hochdruck. Klin. Wschr, 29: 237, 1951.
50 PERERA, G A. The adrenal cortex and hypertension. Bull. N.Y. Acad Med, 26· 75, 1950
51 PICKERING, G. W. The peripheral resistance in persistent arterial hypertension Clin. Sci, 2: 209, 1936.
52 PICKERING, G. W The role of the kidney in acute and chronic hypertension following renal artery constriction in the rabbit. Clin. Sci, 5: 229, 1945
53 PICKERING, G W. High blood pressure. J. & A. Churchill Ltd, London, 1955
54 PICKERING G W and KISSIN M [illegible]
55 PLA[illegible] ... J Med, n s 17: 83, 1948
56 PRINZMETAL, M, and WILSON, C. The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system J. clin Invest, 15: 63, 1936.
57 RAAB, W Die Zentrogenenformen des arteriellen Hochdruckes Ergebn. inn Med Kinderheilk, 46: 452, 1934.
58 RAAB, W Hormonal and neurogenic cardiovascular disorders Williams & Wilkins, Baltimore, 1953
59 RAKITA, L, and SANCETTA S M [illegible] methonium in norm[illegible]
59a ROSS, E J Total exchan[illegible] 15 81, 1956
60 SCHROEDER, H A Hypertensive Diseases, Henry Kimpton, London, 1953.
61 SMIRK, F H Casual and basal blood pressures. IV. Their relationship to the supplemental pressure with a note on statistical implications. Brit Heart J, 6. 176, 1944
62 SMIRK, F H. The pathogenesis of essential hypertension. The Royal Australasian College of Physicians' Pamphlet, Sept., 1946
63 SMIRK, F H. Pathogenesis of essential hypertension Brit med. J., 1: 791, 1949
64 SMIRK, F H, ALSTAD, K. S, KILPATRICK, J A. K. and VEALE, A M. O Unpublished observations 1956
65 SMIRK, F H, and DOYLE, A E. Neurogenic and humoral factors in hypertension Proc Univ Otago med Sch 32: 11 [illegible]
66 SMITH, H W [illegible] H A [illegible] unoper[illegible]
67 TEN[illegible]
68 TOB[illegible] DIXON, J. T. Tissue cations and water in arterial hypertension Circulation (N Y). 5. 754, 1952
69 VEALE, A M O, IRVINE, R O H, and HAMILTON, M. 1956, to be published
70 VEALE, A M O., HAMILTON, M, IRVINE, R. O H, and SMIRK, F H. Casual and near basal pressures in a population survey. Proc Univ. Otago med Sch, 34 20, 1956
71 VOLHARD, F. On the pathogenesis of red (essential) arterial hypertension and of malignant nephrosclerosis. Stanford med Bull., 6· 13, 1948.

effect of hexamethonium bromide on the cardiac output and pulmonary circulation. Lancet, 2. 898, 1952.

29 GOLLWITZER-MEIER, K. Veränderungen der Kohlensäurespannung in ihrer [illegible] 1929

30 GÖM [illegible] Z

31 GREGORY, R [illegible] W. C. Studies on hypertension. V. Effect of high spinal a [illegible] and far- [illegible] sis of hypertension. J. Lab. clin. Med., 30· 1037, 1945

32 GREISMAN, S E. The reaction of the capillary bed of the nailfold to the continuous intravenous infusion of levo-nor-epinephrine in patients with normal blood pressure and with essential hypertension J. clin. Invest., 33: 975, 1954.

33 GROLLMAN, A. The pathogenesis and treatment of hypertension. J. Amer Geriatrics Soc., 1: 223, 1953.

33a HAJDU, S., and LEONARD, E. The action of human plasma on the isolated frog heart 48th Annual Meeting of the Amer Soc Clin. Invest, April 30th, 1956, p. 26

34 HAMILTON, M., PICKERING, G W., ROBERTS, J A. F., and SOWRY, G S C The aetiology of essential hypertension IV The role of inheritance Clin Sci, 13 273, 1954

35 HINES, E. A, Jr., and BROWN, G E A standard stimulus for measuring vasomotor reactions: Its application in the study of hypertension Proc. Mayo Clin, 7: 332, 1932

36 HINES, E A., and BROWN, G E A standard test for measuring the variability of blood pressure Its significance as index of the prehypertensive state Ann intern Med, 7 209, 1933

37 HINES, E A, Jr, and BROWN, G E. The hereditary factor in the reaction of blood pressure to a standard stimulus (cold) — Preliminary report Proc Mayo Clin., 10. 371, 1935.

38 KEYS, A. Symposium. Atherosclerosis Second World Congress of Cardiology, Washington D C, 1954.

39 KEZDI, P. Sinoaortic regulatory system — Role of pathogenesis of essential and malignant hypertension Arch intern Med, 91· 26, 1953

40 KEZDI, P. Neurogenic hypertension in man in porphyria — Transient hypertension and tachycardia caused by disruption of the carotid sinus — Review of buffer nerve mechanism Arch intern Med, 94· 122, 1954

41 KOWALSKI H J, HOOBLER, S W., MALTON, S D, and LYONS, R. H [illegible] hypertension

42 LACI [illegible] Lehre. [illegible]

43 LANDIS, E M, and HORTENSTINE, J C Functional significance of venous blood pressure. Physiol Rev, 30: 1, 1950

43a MJA [illegible] of the hypertensive disease. Acta

44 McQ. [illegible] unpublished observations.

45 McQUEEN, E G, and VEALE, A M O Vascular reactivity in renoprival hypertension. Proc Univ Otago med. Sch, 33· 34, 1955.

46 MACWILLIAM, J. A. Blood pressures in man under normal and pathological conditions Physiol Rev, 5· 303, 1925

47 MENDLOWITZ, M Digitalis vascular resistance in normal, polycythemic and hypertensive states Circulation (N Y), 3: 694, 1951.

CHAPTER XII

# PROGNOSIS OF HYPERTENSION

(in the absence of definitive treatment)

A survey of the literature concerning the prognosis of hypertension may seem to present a confusing picture, for the experiences of some authors point to a good, and of others to a gloomy, prognosis. When, however, attention is given to the way the patients have been assembled, a consistent pattern emerges, for there are methods of collecting patients for study which favour the selection of patients in an early stage of their disorder, and others lead to the selection of patients who are nearing their end.

Although some patients last only a few years with a rapidly progressive hypertension, many whose casual blood pressures are high, survive fifteen, twenty or even thirty years. In most cases, if the blood pressure is much raised, they develop hypertensive manifestations and eventually die from a disorder which is due to or accelerated by the hypertension; but they may die from an unrelated cause, with or without a diagnosis of hypertension.

## RELATIONSHIP IN SURVEYS BETWEEN THE SOURCE FROM WHICH THE PATIENTS HAVE BEEN DERIVED AND PROGNOSIS

Surveys tending to collect together for study patients who are in an asymptomatic stage of hypertension give the impression of a good prognosis; and surveys which only collect patients in a late or dangerous stage reveal a bad prognosis. I have arranged in order various types of surveys, starting with those likely to discover hypertension in its asymptomatic stages and ending with those in which the cases studied are likely to have a poor outlook.

1. Population surveys, life insurance examinations, student health clinics, industrial health examinations, periodic examinations at life extension institutes, etc.
2. Surveys by general practitioners on the basis of routine blood pressures taken because of an interest in the subject.
3. Surveys by general practitioners on the basis of blood pressures taken for suggestive symptoms.

72 VOLHARD, F. Die Pathogenese des Hochdrucks. Verh dtsch. Ges Kreisl-Forsch., 15: 40, 1949.

73 WERKÖ, L., FRISK, A. R, WADE, G., and ELIASCH, H Effect of hexamethonium bromide in arterial hypertension. Lancet, 2: 470, 1951

74 WHITE, P. D. Cardiovascular epidemiology. Second World Congress of Cardiology, Washington D. C., 1954.

75 WIGGERS, C. J. The influence of vascular factors on mean pressure, pulse pressure and phasic peripheral flow. Amer. J. Physiol, 123. 644, 1938

76 WILSON, C., and BYROM, F. B. The vicious circle in chronic Bright's disease — Experimental evidence from the hypertensive rat. Quart. J. Med., n.s. 10: 65, 1941.

77 WOL

78 WOLLHEIM, E. Eine neue körpereigene blutdrucksenkende Substanz und ihre Bedeutung für die essentielle Hypertonie. Acta med. scand., 91: 1, 1937.

79 WOLLHEIM, E. Gefässerweiternde Stoffe des Harns und Renin Acta physiol. scand, 10: 126, 1945

prising twelve 5-year age groups under age 60. Hypertension was defined as over 150/90 mm. Hg. Evidently a considerable amount of hypertension, as here defined, occurs without its existence being realized by the individuals concerned, or by a doctor if one has been consulted. Most of the hypertensive persons whose condition deteriorates will be diagnosed later. The lapse of time between diagnosis and

| Exact age $x$ (1) | Number dying with hypertension between exact age $x$ and $x+5$ (6) | | Chances in 100 of acquiring hypertension between exact age $x$ and $x+5$ (7) | | Chances in 100 of acquiring hypertension between exact age $x$ and $x+1$ (8) | | Chances in 100 of ever acquiring hypertension after exact age $x$ (9) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 | (¹) | (¹) | (¹) | (¹) | (¹) | (¹) | (¹) | (¹) |
| 5 | 11 | 6 | < 005 | 02 | (²) | .01 | 46 36 | 53 51 |
| 10 | 16 | 13 | 06 | 07 | .01 | .01 | 46 64 | 53 75 |
| 15 | 40 | 28 | .13 | .21 | 02 | .03 | 46 88 | 53 94 |
| 20 | 72 | 44 | 18 | .26 | .03 | .05 | 47.25 | 54 24 |
| 25 | 109 | 59 | .28 | .33 | 04 | .06 | 47.78 | 54 66 |
| 30 | 162 | 104 | 37 | 58 | .06 | .09 | 48 30 | 55.16 |
| 35 | 254 | 210 | 54 | 1 00 | 09 | .17 | 48 93 | 55 68 |
| 40 | 450 | 424 | .98 | 1 63 | .15 | .24 | 49 72 | 56 20 |
| 45 | 794 | 864 | 1 56 | 2 75 | .26 | .49 | 50 72 | 56 69 |
| 50 | 1,379 | 1,530 | 2.70 | 3 51 | 45 | .65 | 52 03 | 56 99 |
| 55 | 2,358 | 2,386 | 4 47 | 4 53 | .77 | .64 | 53 82 | 57.38 |
| 60 | 3,783 | 3,475 | 7.16 | 6.19 | 1 23 | 1 11 | 55 92 | 58 04 |
| 65 | 5,536 | 5,044 | 10 98 | 9 01 | 2 05 | 1.65 | 58.16 | 59.14 |
| 70 | 6,965 | 7,414 | 15 73 | 13 54 | 3 01 | 2 60 | 60 38 | 60 84 |
| 75 | 7,919 | 8,974 | 23 76 | 18 78 | 4 72 | 3 84 | 63 65 | 63 22 |
| 80 | 7,823 | 9,733 | 39 87 | 32 44 | 8 35 | 5 82 | 67.75 | 68.60 |
| 85 | 6,390 | 9,775 | 61 44 | 70 62 | 14 99 | 14 67 | 61.44 | 70 62 |
| 90 | | . | | | | .. | ... | ... |

death will be less than the time between the onset of symptomless *hypertension and death from whatever cause.* The application of the results of surveys to individual prognosis obviously needs great care.

Woolsey (1950) gives the results of the national health survey of diagnosed hypertension which was conducted in the United States in 1935—1936.

The graph (Fig. XII 1) derived from the figures in W[illegible] (Table XII 1) [illegible]
hypertension [illegible]
taneously an [illegible] points on the graph which have reference to ages 60 to 65 are concerned with those in-

* The American cohort (100,000) is apparently larger than the Roman cohort (500)

TABLE XII 1. *Crude abridged life table showing how many out of 100,000 infants of each sex can be expected to acquire hypertension between specified birthdays; and certain other measures of hypertension incidence and mortality from the life table*

(See text for complete description)
(Woolsey, T. D. Publ. Hlth Rep. (Wash.), 65: 555, 1950)

| Exact age $x$ (1) | Prevalence of hypertension (per head) at exact age $x$ (National Health Survey) (2) | | Number still living at exact age $x$ (1939—41 life table) (3) | | Number living at exact age $x$ who have hypertension (4) | | Number acquiring hypertension between exact age $x$ and $x+5$ (5) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 | 0 | 0 | 100,000 | 100,000 | 0 | 0 | (1) | (1) |
| 5 | .00030 | 00015 | 93,624 | 94,848 | 28 | 14 | 3 | 19 |
| 10 | .00022 | 00030 | 93,054 | 94,402 | 20 | 28 | 54 | 68 |
| 15 | .00064 | 00090 | 92,508 | 94,000 | 59 | 85 | 117 | 197 |
| 20 | .00148 | 00270 | 91,617 | 93,293 | 136 | 252 | 169 | 246 |
| 25 | .00258 | .00490 | 90,385 | 92,322 | 233 | 452 | 233 | 307 |
| 30 | 00400 | .00765 | 89,009 | 91,182 | 356 | 698 | 330 | 529 |
| 35 | .00600 | 01250 | 87,371 | 89.810 | 524 | 1,123 | 471 | 887 |
| 40 | 00870 | .02045 | 85,246 | 88,092 | 742 | 1.801 | 828 | 1,404 |
| 45 | .01360 | 03240 | 82,336 | 85,856 | 1,120 | 2,782 | 1 263 | 2,281 |
| 50 | 02030 | 05070 | 78.254 | 82,828 | 1,589 | 4,109 | 2,070 | 2,781 |
| 55 | 03140 | 06900 | 72,627 | 78 709 | 2,280 | 5,431 | 3,147 | 3,320 |
| 60 | 04710 | 08710 | 65,142 | 73,093 | 3,068 | 6,366 | 4,441 | 4,133 |
| 65 | .06680 | 10720 | 55,776 | 65,523 | 3,726 | 7,024 | 5,715 | 5,273 |
| 70 | 08760 | .13080 | 44,588 | 55,449 | 3,906 | 7,253 | 6,399 | 6,526 |
| 75 | .10485 | 15000 | 31,864 | 42 425 | 3,341 | 6,364 | 6.778 | 6,772 |
| 80 | .11580 | 15120 | 18,095 | 27 524 | 2,200 | 4,162 | 6,697 | 7,578 |
| 85 | .12360 | .14380 | 8,693 | 13,972 | 1,074 | 2,009 | 4,681 | 8,448 |
| 90 | . | . . | 2,787 | 5,044 | 365 | 681 | . | . . |

[1] Values for ages from birth to 5 years considered too unreliable to be useful
[2] Number of new cases turned out to be negative See text.

4. *Surveys based on cases referred to a consultant*, or cases collected from hospital outpatient departments and not necessarily referred for hypertension.
5. Surveys based on cases referred for hypertension.
6. Patients admitted to hospital for hypertensive manifestations.

Collins (1949), in a government survey covering all classes of cases, estimated that the prevalence of diagnosed hypertension in the United States was 4,600,000 cases in a population of 149,200,000; 3.1 per cent *including persons over 60. In the Federal survey of farm families by* Gover (1948) in which blood pressures were measured routinely, there was a 10.7 per cent incidence of hypertension among individuals com-

prising twelve 5-year age groups under age 60. Hypertension was defined as over 160/90 mm. Hg. Evidently a considerable amount of hypertension, as here defined, occurs without its existence being hypertension, as ... individuals concerned or by a doctor if one has been

| Exact age $x$ (1) | Number dying with hypertension between exact age $x$ and $x+5$ (6) | | Chances in 100 of acquiring hypertension between exact age $x$ and $x+5$ (7) | | Chances in 100 of acquiring hypertension between exact age $x$ and $x+1$ (8) | | Chances in 100 of ever acquiring hypertension after exact age $x$ (9) | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 | (1) | (1) | (1) | (1) | (1) | (1) 01 | (1) 46 36 | (1) 53 51 |
| 5 | 11 | 6 | < 005 | .02 | (1) | .01 | 46 64 | 53 75 |
| 10 | 16 | 13 | 06 | 07 | 01 | 03 | 46 88 | 53 94 |
| 15 | 40 | 28 | 13 | 21 | 02 | 05 | 47.25 | 54 21 |
| 20 | 72 | 44 | 18 | 26 | 03 | .06 | 47 76 | 54 66 |
| 25 | 103 | 59 | 28 | .33 | 04 | 09 | 48 30 | 55.16 |
| 30 | 182 | 104 | .37 | 58 | 06 | .17 | 48 93 | 55 68 |
| 35 | 254 | 210 | .54 | 1 00 | 09 | .24 | 49 72 | 56 20 |
| 40 | 450 | 424 | 98 | 1 63 | 15 | 49 | 50 72 | 56 69 |
| 45 | 794 | 864 | 1 56 | 2 75 | 26 | 65 | 52 08 | 56 09 |
| 50 | 1,379 | 1,530 | 2 70 | 3 51 | .45 | 84 | 53 82 | 57 38 |
| 55 | 2,358 | 2,386 | 4 47 | 4 53 | 77 | 1.11 | 55.82 | 58 04 |
| 60 | 3,783 | 3,475 | 7 16 | 6.19 | 1 23 | 1 65 | 58 16 | 59.14 |
| 65 | 5,536 | 5,044 | 10 98 | 9 01 | 2 05 | 2 50 | 60 36 | 60 84 |
| 70 | 6,965 | 7,414 | 15 73 | 13 54 | 3 01 | 3 84 | 63 65 | 63 22 |
| 75 | 7,919 | 8,974 | 23 76 | 18 78 | 4 72 | 5 82 | 67 75 | 69 60 |
| 80 | 7,823 | 9,733 | 39 87 | 32 44 | 8 35 | 14 67 | 81 44 | 70 62 |
| 85 | 5,390 | 9,775 | 61 44 | 70 62 | 14 99 | .. | . . | .. |
| 90 | | | | | | | | |

death will be less than the time between the onset of symptomless hypertension and death from whatever cause. The application of the results of surveys ...

Woolsey (1... diagnosed hyp... in the United States in 1935—1936.

The graph (Fig XII 1) derived from the figures in Woolsey's table (Table XII 1) represents what should ... hypertension and death to a ... taneously and followed until ... the points on the graph which have reference to ages 60 to 65 are concerned with those in-

* The American cohort (100,000) is apparently larger than the Roman cohort (500)

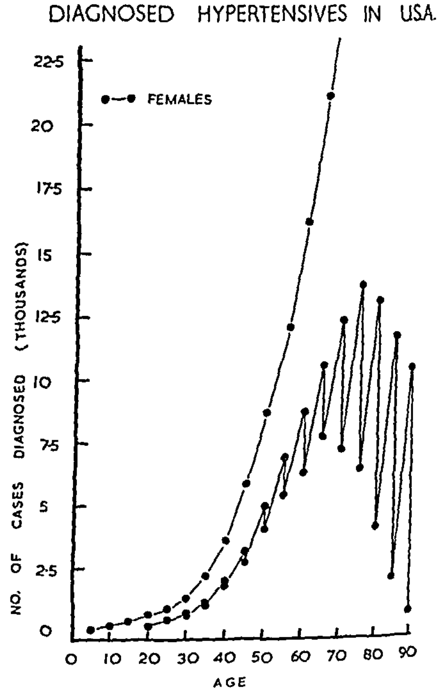



Fig XII 1 a

*Expectation of the occurrence of diagnosed hypertension at various ages among a cohort of 100,000 female infants born simultaneously and followed until death*

The lower, serrated graph sets out the gains and losses in the number of diagnosed hypertensives in each 5 year period Gains are by additional cases diagnosed, losses are by deaths.

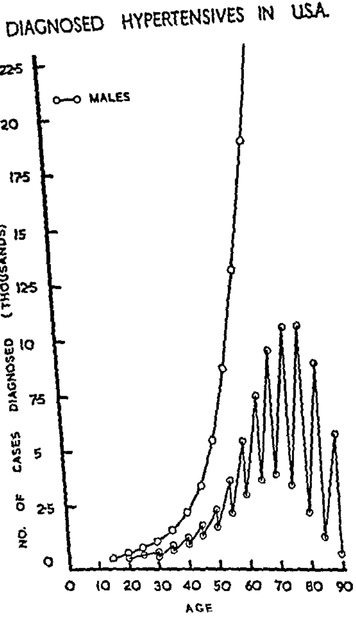



Fig XII 1 b

hypertension than die with hypertension After 65 the number of deaths in each 5 year period exceed the number of new cases diagnosed

dividuals alive at 60 *with* hypertension, those acquiring hypertension between ages 60 and 65, and those dying between 60 and 65. It can be seen from the graph that up to 65 or 70 years of age in males and females the number of persons acquiring hypertension in any 5-year period is in excess of the number who die *with** hypertension.

Up to the age of 70, the number of hypertensives who occupy each successive age group increases, but after the age of 70 the number of deaths of persons with hypertension in each 5-year period exceeds the number acquiring diagnosed hypertension during that period. *Hence, after that age the number in any age group who have diagnosed hypertension falls.* It should be emphasized that the points on the graph relate to the number of persons in each age group (out of 100,000 children born alive) who have diagnosed hypertension. After age 70, although the number with hypertension in successive age groups is falling, there is a rise in the percentage of persons with hypertension. These statistics provide one of the most valuable indications of the outlook of diagnosed hypertension because they cover diagnosed hypertension in all its stages, and are probably less affected by errors of selection than are most statistics on the subject. The average length of *life remaining decreases with advancing age and is less in males* than in females. The survey indicated that where a history was available hypertension had been present already for longer than five years in 38 per cent of cases, and for longer than ten years in 17 per cent (Collins, 1949). Some of the factors follow which concern individual prognosis.

## EFFECT OF SEX

*It is generally agreed that women tolerate high blood* pressure better than men. The following table sets out the mortality in females expressed as a percentage of the mortality in males, according to a number of authors.

The variation in the relative mortalities of males and females (Table XII 2) depends on the length of time a group of cases has been followed, the severity of the cases and the age of the patients. Obviously if cases are followed for a very long time there are few survivors, and the difference between percentages of those who have died decreases. Similarly, in the Keith Wagener series where most of the cases were malignant hypertension or grade 3 cases, there were comparatively few survivors after six years. The survey by Woolsey (Table XII 1) probably gives the most representative account of the difference in mortalities of males and females among diagnosed cases. The inferiority of the male sex becomes even more conspicuous when one takes account of the fact that basal blood pressures tend to be higher in women than in men.

* This does not imply that death was necessarily connected with the hypertension.

The general impression from Rasmussen and Bøe (1945) and Griep et al

in men and 12.5 per cent in women In cerebral vascular accidents they found 30 per cent in men and 18 per cent in women. Aside from hypertension, coronary disease is much more frequent in men than in women. In hypertensives the difference is still present but seems to be reduced.

TABLE XII 2. *Mortality in hypertensive women expressed as a percentage of the mortality in hypertensive men*

| | Per cent |
|---|---|
| Janeway (1913) | 80 |
| Paullin (1926) | 18.5 |
| Weitz and Sieben (1926) | 54 |
| Blackford, Bowers and Baker (1930) | 55 |
| Keith, Wagener and Barker (1939) | 94 |
| Rasmussen and Bøe (1945) | 63 |
| Bechgaard (1946) | 54 |
| Burgess (1948) | 85 |
| Palmer, Loofbourow and Doering (1948) | 72 |
| Collins (1949) | 46.5 |
| Frant and Groen (1950) | 58.5 |
| Hammarstrom and Bechgaard (1950) | 54 |
| Griep et al. (1951) | 63 |
| Leishman (1953) | 55 |

## EFFECT OF OBESITY

In groups of persons representative of the general population, obesity has an adverse effect on mortality and is associated with a higher incidence of hypertension and of coronary artery disease. Overweights whose abdominal girth measurements exceed their expanded chest girths are subject to an additional mortality (Dublin and Marks, 1951) In patients, however, who present as cases of hypertension, obesity does not seem to worsen the prognosis and for similar degrees of elevation of the blood pressure seems to be associated with a more favourable outcome.

Among ...

... In women it was 57 per cent for obese women and 112 per cent for non-obese women. Bechgaard (1946)

has had the same experience. A likely explanation is that the blood pressure is somewhat overestimated in the obese because of the effect of increased girth of the arm on cuff measurements (Wood, 1950; Leishman, 1953). Furthermore, weight reduction offers a therapeutic approach, so that at equal blood pressure levels the obese person may be more favourably situated.

## EFFECT OF THE AGE OF ONSET

The age o [illegible] agreed that [illegible] is much less [illegible] gave their estimate of the relationship between the age of diagnosis and the death rate in essential hypertension. They give the following figures:

TABLE XII 3. *Age and Death Rate in Essential Hypertension* (Frant, R., and Groen, J. Arch. intern. Med., 85: 727, 1950)

| Age, years | Cases | Deaths | | Excess Mortality, % |
|---|---|---|---|---|
| | | Observed | Expected | |
| Men | | | | |
| 40—49 | 28 | 13 | 1.6 | +712 5 |
| 50—59 | 30 | 10 | 5.5 | + 81 |
| 60—69 | 33 | 15 | 10.8 | + 39 |
| 70 and over | 12 | 6 | 8 | — 25 |
| Women | | | | |
| 40—49 | 58 | 11 | 3.5 | +210 |
| 50—59 | 88 | 18 | 11.6 | + 55 |
| 60—69 | 45 | 23 | 10.5 | +119 |
| 70 and over | 6 | 4 | 2.15 | + 86 |

It will be noted in the table from Frant and Groen (1950) and in Figure XII 1, that the mortality rises with age in hypertensives, as it does in normotensives. The difference between the mortalities of hypertensives and normotensives decreases as age advances Palmer and Muench (1953), on the basis of an observation period exceeding ten years, also find that the ratio of observed to expected deaths is higher in young than in older hypertensives (Table XII 4).

Burgess (1948) and Bechgaard, Kopp and Nielsen (1954) find that the younger the patient at the time when the hypertension develops, the less likely he is to live out his full life span. In the under 50 group, however, the average length of life is probably over fifteen years.

Malignant hypertension, though it seldom complicates essential hypertension before age 35, has its highest incidence in patients between 35 and 55, whereas essential hypertension of the benign variety occurs chiefly after age 50. Pickering (1955) considers that the peak incidence of the malignant phase is usually about 40 years. In our own series and that of Palmer et al (1948) the peak incidence is in the 40 to 49 age group.

TABLE XII 4. *Ratio of Observed to Expected Deaths by Person Years* (Palmer, R. S., and Muench, H. J. Amer. med. Ass., **153**: 1, 1953)

| Age, Year | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|
| | Men | Women | Men | Women | Men | Women | Men | Women |
| 0—34 | 15.4 | 11.6 | — | 68.8 | 183.1 | 101.6 | 331.8 | 298.4 |
| 35—54 | 4.3 | 4.9 | 3.8 | 9.6 | 32.1 | 34.7 | 84.4 | 119.3 |
| 55—74 | 2.9 | 0.7 | 3.9 | 2 6 | 6.2 | 4.9 | 80 6 | 28.9 |
| 75 plus | 7 2 | 0.5 | — | 0.8 | 2.5 | 1.4 | — | — |
| Total | 3.8 | 1.3 | 3.9 | 2.7 | 9.4 | 5.6 | 100.1 | 139.3 |
| Persons | 40 | 70 | 29 | 59 | 99 | 102 | 32 | 22 |
| Person years | 349 | 680 | 190 | 472 | 349 | 515 | 36 | 37 |
| Mean age* | 44 2 | 47 0 | 53.5 | 52.6 | 52.6 | 55.0 | 39 2 | 38.5 |

* Based on age at entry to series

Palmer grades 1, 2, 3, 4 in the above table are in ascending order of severity. Grade 4 is malignant hypertension. Further detail is given in Chapter XIV.

## EFFECT OF THE LEVEL OF THE CASUAL BLOOD PRESSURE

It is generally ... 1950, ... outlo ... a close relatio ... blood pressur ... hypertensi ... study of the life ... average 9. In a hospital inpatient series the duration of life would have been much less.

## Life Insurance Statistics

Some tables follow which set out the relationship between elevated blood pressure and life expectancy:

TABLE XII 5.
(Medical Impairment Study, 1929)

| Age | Normal systolic blood pressure | Blood pressures corresponding to certain mortalities which are expressed as a percentage of the usual expected mortality | | |
|---|---|---|---|---|
| | | 153 % | 181 % | 216 % |
| 15—29 years | 120 | 125 to 135 | 136 to 144 | 145 and over |
| 30—44 ,, | 125 | 130 to 140 | 141 to 149 | 150 |
| 45—53 ,, | 130 | 135 to 145 | 146 to 154 | 155 |
| 54—70 ,, | 135 | 140 to 150 | 151 to 159 | 160 |

TABLE XII 6. *Statistics Based on 34,826 Cases*
(Medical Impairment Study, 1929)

| Rise of systolic blood pressure above normal | Mortality expressed as a percentage of the usual expected mortality |
|---|---|
| 5 to 15 mms | 153 % |
| 16 to 24 ,, | 181 % |
| 25 to 34 ,, | 205 % |
| 35 to 44 ,, | 265 % |
| 45 mms. and over | 384 % |

TABLE XII 7. *Compiled by American and Canadian Insurance Companies*
(Trans. Internat. Congress Life Ass. Med., Lond., 1935)

| Systolic | 135 | 140 | 145 | 150 | 155 | 160 | 165 | 170 |
|---|---|---|---|---|---|---|---|---|
| Diastolic | 92 | 95 | 98 | 100 | 102 | 104 | — | — |
| Age 20 years and less | 5 | 10 | 20 | 35 | 55 | 80 | 105 | 135 |
| 25 | 5 | 10 | 20 | 35 | 55 | 80 | 110 | 145 |
| 30 | 5 | 15 | 25 | 40 | 60 | 85 | 115 | 155 |
| 35 | 10 | 20 | 30 | 45 | 65 | 90 | 120 | 160 |
| 40 | 10 | 20 | 30 | 50 | 70 | 100 | 130 | 170 |
| 45 | 10 | 20 | 30 | 50 | 70 | 95 | 125 | 165 |
| 50 | 10 | 15 | 25 | 45 | 65 | 90 | 120 | 155 |
| 55 | 5 | 10 | 20 | 35 | 50 | 75 | 100 | 130 |
| Age 60 years and over | 0 | 5 | 15 | 20 | 30 | 50 | 75 | 100 |

The figures indicate the percentage degree to which the actual mortality exceeds the expected mortality.

TABLE XII 8. *Prudential Life Insurance Society*
(May, 1925)

| Systolic pressure | Mortality |
|---|---|
| Under 140 | 102 8 |
| 140—170 | 133.6 |
| Over 170 | 219.6 |
| Over 200 | 827.5 |

## The Significance of Minor Casual Blood Pressure Elevations in Youth and Early Adult Years

The statistics from
that those who exh
have an importan ... towards the development later of
essential

... than the average have a higher than average incidence of hypertension and circulatory disorder *in later life,* whereas those whose pressures are below the average have a decidedly lower than average incidence of essential hypertension and of circulatory disorders in later life [1, 3, 4, 13, 26, 27, 28, 30, 31, 58].

Individuals whose blood pressure rises high on occasion, though falling later to normal limits, have an enhanced tendency to develop essential hypertension *in later life.* Such temporary
often of

tl
n
T ... of the assurance companies (Frost, 1926, MacKenzie and Shepherd, 1937) and on American university students (Palmer, 1930; Diehl and Hesdorffer, 1933) Robinson and Brucer (1939) reach the same conclusion on the basis of figures which combine life insurance and student groups.

The
of
cor ... The occurrence of transient ... are of
as of transient
the greater like
Among the grou
sustained hyper

## Life Insurance Statistics

Some tables follow which set out the relationship between elevated blood pressure and life expectancy:

TABLE XII 5.
(Medical Impairment Study, 1929)

| Age | Normal systolic blood pressure | Blood pressures corresponding to certain mortalities which are expressed as a percentage of the usual expected mortality | | |
|---|---|---|---|---|
| | | 153 % | 181 % | 215 % |
| 15—29 years | 120 | 125 to 135 | 136 to 144 | 145 and over |
| 30—44 ,, | 125 | 130 to 140 | 141 to 149 | 150 |
| 45—53 ,, | 130 | 135 to 145 | 146 to 154 | 155 |
| 54—70 ,, | 135 | 140 to 150 | 151 to 159 | 160 |

TABLE XII 6. *Statistics Based on 34,826 Cases*
(Medical Impairment Study, 1929)

| Rise of systolic blood pressure above normal | Mortality expressed as a percentage of the usual expected mortality |
|---|---|
| 5 to 15 mms. | 153 % |
| 16 to 24 ,, | 181 % |
| 25 to 34 ,, | 205 % |
| 35 to 44 ,, | 265 % |
| 45 mms. and over | 384 % |

TABLE XII 7. *Compiled by American and Canadian Insurance Companies*
(Trans. Internat. Congress Life Ass. Med., Lond., 1935)

| Systolic | 135 | 140 | 145 | 150 | 155 | 160 | 165 | 170 |
|---|---|---|---|---|---|---|---|---|
| Diastolic | 92 | 95 | 98 | 100 | 102 | 104 | — | — |
| Age 20 years and less | 5 | 10 | 20 | 35 | 55 | 80 | 105 | 135 |
| 25 | 5 | 10 | 20 | 35 | 55 | 80 | 110 | 145 |
| 30 | 5 | 15 | 25 | 40 | 60 | 85 | 115 | 155 |
| 35 | 10 | 20 | 30 | 45 | 65 | 90 | 120 | 160 |
| 40 | 10 | 20 | 30 | 50 | 70 | 100 | 130 | 170 |
| 45 | 10 | 20 | 30 | 50 | 70 | 95 | 125 | 165 |
| 50 | 10 | 15 | 25 | 45 | 65 | 90 | 120 | 155 |
| 55 | 5 | 10 | 20 | 35 | 50 | 75 | 100 | 130 |
| Age 60 years and over | 0 | 5 | 15 | 20 | 30 | 50 | 75 | 100 |

and bring the blood pressure into a so-called normal range. It is, however, a mistake, as our survey shows, to regard a fixed level of the blood pressure as "normal". The transient hypertensive with reassurance and repeated blood pressure measurement has his blood pressure reduced to a level which is "normal" for a person who has not been reassured nor had repeated measurements. Were the blood pressure of the "transient hypertension" case obtained on a second visit compared with the level for normals, also taken with a similar rest period on a second visit, the difference between the readings in many cases would not be altered.

In so-called transient hypertension cases the basal blood pressure may be high and the supplemental pressure normal, the fall of blood pressure with rest and reassurance is then due to decrease in a normal supplemental pressure.

The life insurance figures quoted earlier, which relate the average level of the casual blood pressure to the expectation of death or of disability are highly significant, but individual prognosis is much more difficult. Our survey (Chapter III) indicates the dependence of the blood pressure le

... on a high casual blood pressure, much unnecessary apprehension and distress of patients or their relatives can be avoided.

### The Significance of Casual Blood Pressure Elevation in Elderly People

Monroe (1951) emphasizes the benign character of the hypertension encountered in a geriatric clinic attended by patients over the age of 65 Droller et al (1952) give their experience in Sheffield with 476 elderly people living at home, the ages being 60 and above. They were impressed by the comparative fitness of the group and their impression was that the hypertension, in the majority of instances, was causing little disability.

ret

ros

grc

... he considers as substantially normal in older people. It did not increase the mortality beyond that normally expected, whereas diastolic hypertension increased the mortality.

My own impression is that hypertension in elderly individuals is usually more benign than in middle-aged

b

P ... whose blood pressure is discovered incidentally or who, for one or more reasons, have become attached to a geriatric clinic. ...hypertensive clinic and elderly

z

transient hypertension 19.4 per 1000 later developed sustained hyper-tension. This [illegible]
groups and, [illegible]
per 1000; namely, 3.6 times as high as the group which did not exhibit transient hypertension.

Officers who had exhibited neither transient hypertension nor transient tachycardia had a rate for the subsequent development of sustained hypertension of 2.5 per 1000. In officers showing both transient tachycardia and transient hypertension the incidence of subsequent sustained hypertension was 7.5 times as large as when both were absent.

Deaths and disability retirement from cardiovascular causes were much higher among officers exhibiting either transient hypertension or tachycardia than among officers who exhibited neither of these.

Master (1943) drew corresponding conclusions on the basis of United States naval personnel. Such statistics do not show that all individuals who have exhibited transient hypertension may expect sooner or later to develop clinical hypertension. This only occurs in a proportion of instances. A wealth of information, however, testifies to the fact that the occurrence of moderate blood pressure elevation or transient hypertension is associated with an important increase in the expectation of sustained hypertension and of disabilities and death in later life.

The greater incidence of sustained hypertension in later life among those who exhibit transient elevations at an earlier date has been observed in a clinical setting by von Monakow (1920); Stieglitz (1930) and Hines (1940). Fishberg (1954) says "the writer has for many years been convinced that *at least the larger moiety of individuals exhibiting such transitory "emotional" hypertension ultimately prove to have essential hypertension*, although it may be decades before this is evident".

Our survey (Chapter III) throws some light on the significance of transient blood pressure rises of the type referred to in life insurance statistics and in various student surveys. It has been pointed out many times that life insurance applicants or persons attending for a blood pressure measurement for a survey may exhibit an overaverage blood pressure, but when called back for a further blood pressure measurement, and perhaps reassured, they exhibit a value within normal limits. It is sometimes assumed that the reason for this is that the patient has an unusually labile blood pressure and has risen to a larger extent than the average, and that the "true" blood pressure is "normal". This may be so in some cases but it is an unjustifiable generalization. The rise of blood pressure on first contact with a doctor may be sufficiently great to bring the blood pressure level into an arbitrary range which is called abnormal. Reassurance and repeated measurement of the blood pressure may subtract 20 mm. systolic and 10 mm. diastolic

... into a so-called normal range. It is, ...

lood pressure as normal ...
ssurance and repeated blood pressure measurement has ...
oressure reduced to a level which is "normal" for a person who has not been reassured nor had repeated measurements. Were the blood pressure of the "transient hypertension" case obtained on a second visit compared with the level for normals, also taken with a similar rest period on a second visit, the difference between the readings in many cases would not be altered.

In so-called transient hypertension cases the basal blood pressure may be high and the supplemental pressure normal, the fall of blood pressure with rest and reassurance is then due to decrease in a normal supplemental pressure.

The life insurance figures quoted earlier, which relate the average level of the casual blood pressure to the expectation of death or of disability are highly significant, but individual prognosis is much more difficult Our survey (Chapter III) indicates the dependence of the blood pressure level on comparatively slight differences in the circumstances surrounding its measurement. If adverse individual prognoses ... necessary

## The Significance of Casual Blood Pressure Elevation in Elderly People

... the benign character of the hypertension ... patients over the age of ... in Sheffield with 476 elderly people living at home, the ages being 60 and above. They were impressed by the comparative fitness of the group and their impression was that the hypertension, in the majority of instances, was causing little disability

Russek (1943) made a blood pressure study in 1000 male subjects, all retired seamen between the ages of 60 and 95. The mean blood pressure ... 157/85 in the age ...

normally expected, whereas diastolic hypertension increased the mortality

My own impression is that hypertension in elderly individuals is usually more benign than in middle-aged persons. Even so, there is a distinctive difference in severity between elderly people who are sent by their doctor to a cardiovascular or hypertensive clinic and elderly people whose blood pressure is discovered incidentally or who, for one or more reasons, have become attached to a geriatric clinic.

Dr. E. Northcroft, of Dunedin, kindly provided me with details of the hypertensive patients seen in his practice during the last five years. These numbered 104, and 48 of them were 70 years or older Seventy-one patients had systolic blood pressures of 200 mm. Hg or more, 43 had diastolic pressures of 110 mm. Hg or more. Fifty-three out of the 104 patients presented with non-hypertensive complaints In general, at least in New Zealand, when a practitioner refers a patient to hospital the pressure is either inordinately high or is occurring at an unusually early age, or clinical manifestations have occurred which have persuaded him that the case is in need of treatment. The outlook of a collection of hospital cases is no guide to the outlook of a collection of general practice cases, which are usually milder.

## RELATIONSHIP BETWEEN BASAL AND SUPPLEMENTAL BLOOD PRESSURES AND PROGNOSIS

It has been pointed out already that the supplemental blood pressure (casual minus basal) has a slightly negative correlation with the basal blood pressure, in the sense that a member of a population with a higher than average level of the basal blood pressure is likely to have a lower than average level of the supplemental blood pressure, and *vice versa*.

It becomes of particular interest to study the relations between the basal and supplemental blood pressures and prognosis separately. As might be expected, the basal blood pressure is a better index of prognosis as regards life expectancy than is the supplemental blood pressure.

Figure XII 2 summarizes the basal and supplemental blood pressures of patients in this five year follow-up series. It will be seen that the deaths are more frequent when the basal blood pressure is high and survival is more frequent when the basal blood pressure is low. The levels of the supplemental pressure, however, are not closely related to life expectancy. If in each age group the average mean basal blood pressure (systolic + diastolic)/2 is taken of those patients who died and compared with the patients who live, it is seen (Fig. XII 3a, b) that the average basal blood pressure of those who died is greater than the average mean basal blood pressure of those who survived.

It was anticipated from the outset that the relationship between the supplemental blood pressure and prognosis would not be as close as between the basal blood pressure and prognosis. The result actually obtained was unexpected — there is a slight negative correlation between supplemental blood pressure and prognosis (Fig. XII 3a, b), in the sense that those with a high level of the supplemental blood pressure may have a slightly better outlook than those with a low level. Presumably the reason for this is not that a high supplemental blood

... favourable in itself, but, being correlated negatively with the ... blood pres- ... ce a some- what more favourable prognosis.

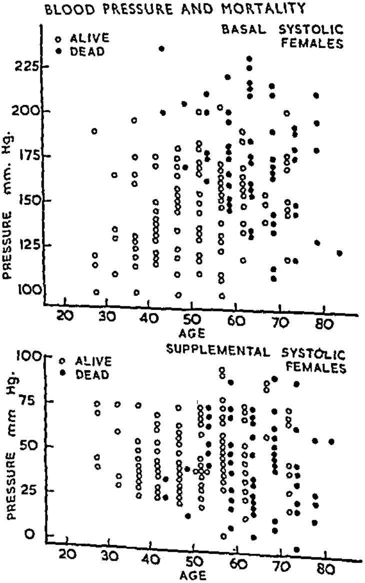



Fig XII 2a

... systolic pressures

Dr. E. Northcroft, of Dunedin, kindly provided me with details of the hypertensive patients seen in his practice during the last five years. These numbered 104, and 48 of them were 70 years or older. Seventy-one patients had systolic blood pressures of 200 mm. Hg or more, 43 had diastolic pressures of 110 mm. Hg or more. Fifty-three out of the 104 patients presented with non-hypertensive complaints In general, at least in New Zealand, when a practitioner refers a patient to hospital the pressure is either inordinately high or is occurring at an unusually early age, or clinical manifestations have occurred which have persuaded him that the case is in need of treatment. The outlook of a collection of hospital cases is no guide to the outlook of a collection of general practice cases, which are usually milder.

## RELATIONSHIP BETWEEN BASAL AND SUPPLEMENTAL BLOOD PRESSURES AND PROGNOSIS

It has been pointed out already that the supplemental blood pressure (casual minus basal) has a slightly negative correlation with the basal blood pressure, in the sense that a member of a population with a higher than average level of the basal blood pressure is likely to have a lower than average level of the supplemental blood pressure, and *vice versa.*

It becomes of particular interest to study the relations between the basal and supplemental blood pressures and prognosis separately. As might be expected, the basal blood pressure is a better index of prognosis as regards life expectancy than is the supplemental blood pressure.

Figure XII 2 summarizes the basal and supplemental blood pressures of patients in this five year follow-up series. It will be seen that the deaths are more frequent when the basal blood pressure is high and survival is more frequent when the basal blood pressure is low. The levels of the supplemental pressure, however, are not closely related to life expectancy. If in each age group the average mean basal blood pressure (systolic + diastolic)/2 is taken of those patients who died and compared with the patients who live, it is seen (Fig. XII 3a, b) that the average basal blood pressure of those who died is greater than the average mean basal blood pressure of those who survived.

It was anticipated from the outset that the relationship between the supplemental blood pressure and prognosis would not be as close as between the basal blood pressure and prognosis. The result actually obtained was unexpected — there is a slight negative correlation between supplemental blood pressure and prognosis (Fig. XII 3a, b), in the sense that those with a high level of the supplemental blood pressure may have a slightly better outlook than those with a low level Presumably the reason for this is not that a high supplemental blood

... measured in a population survey
... the
... of

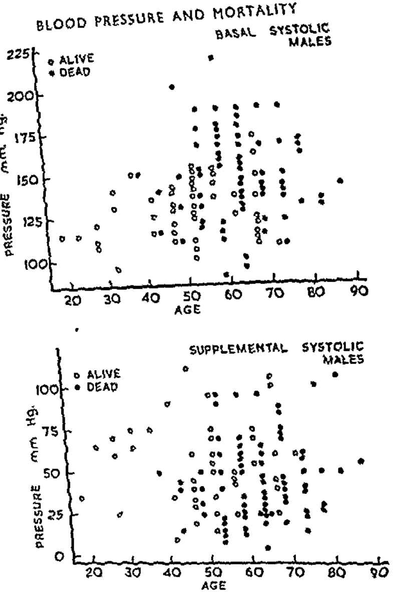



Fig XII 2c

The Figure shows that male patients with high basal systolic blood pressures have a smaller expectation of a 5 year survival than male patients with lower basal systolic blood pressures. Male patients with high supplemental systolic pressures have at least as good an expectation of a 5 year survival as patients with lower supplemental systolic pressures

*It has not been possible as yet to make a sufficiently detailed survey of the normal basal blood-pressures in the population, but certain statements can be made when we consider such results as we have in relation to a series of about 1,000 basal blood pressures in hypertensive*

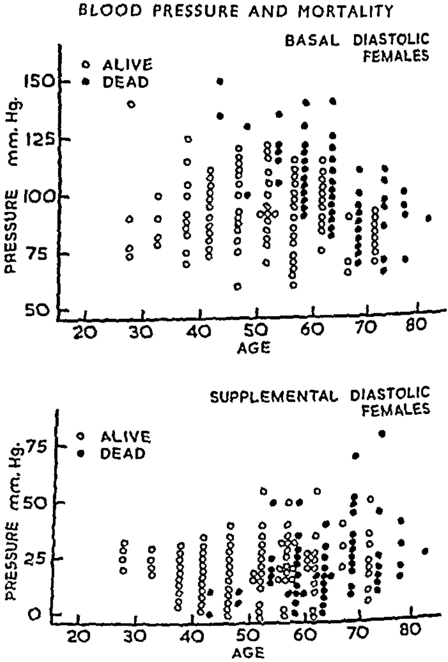



Fig XII 2b

The Figure shows that female patients with high basal diastolic blood pressures have [illegible]

diastolic pressures.

blood pressures, such as 180/120 or 200/130, the outlook is very bad, both in males and females; but at all pressure levels the female tolerates a high basal blood pressure better than the male. The relation-

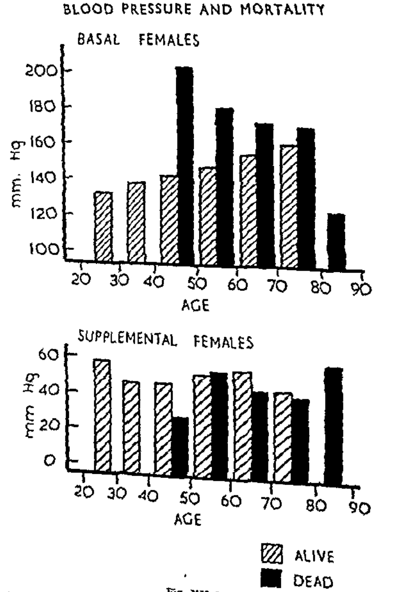



Fig XII 3a

died

the basal blood pressure is somewhat overaverage if it exceeds the mean level of the near-basal blood pressure of persons in the same age

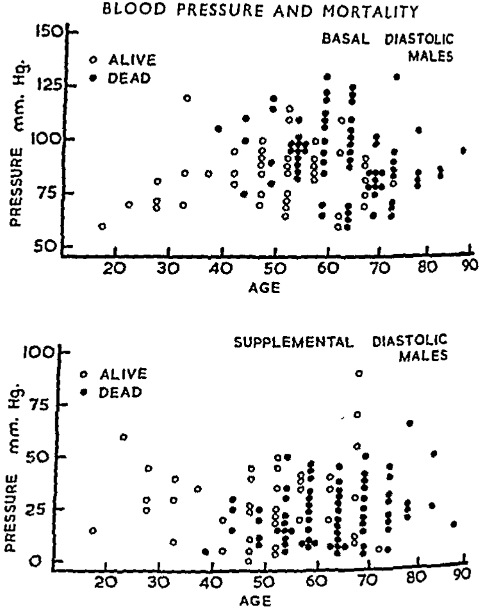



Fig XII 2d

The Figure shows that male patients with high basal diastolic blood pressures have a smaller expectation of a 5 year survival than male patients with lower basal diastolic blood pressures. Male patients with high supplemental diastolic pressures have at least as good an expectation of a 5 year survival as patients with lower supplemental diastolic pressures

group. It can be seen from our follow-up of a series of rather mild hypertensives (Fig. XII 4a) that if the basal systolic blood pressure exceeds 140 or 150 in males or 160 to 170 in females the outlook for a five year survival is noticeably impaired. With very high basal systolic

doctor measures the blood pressure and begins to think about the outlook of the case, he is considering the sum of two variables, namely [illegible] constant for

[illegible]

the blood pressure. This labile fraction of the blood [illegible]

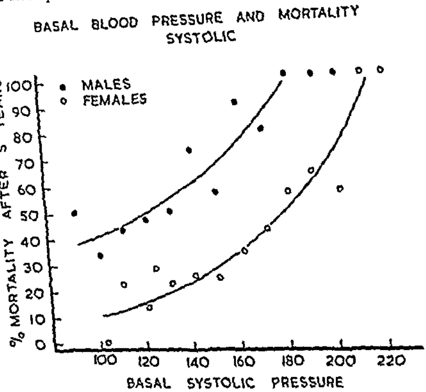



Fig XII 4a

Relationship between [illegible] after 5 years It will b[illegible] sure the percentage [illegible]

value as an indication of the severity of the case. Two patients may exhibit identical blood pressures in the doctor's office, say 200/120 mm Hg When the basal blood pressure is determined the one patient may have a basal blood pressure of 175/115, the other a basal blood pressure of 130/85 Neither of these results is unusual. The patient with the low basal blood pressure probably has a good outlook; the patient with the high basal blood pressure has a bad prognosis.

The experience of our clinic is that prognosis based on the casual blood pressure (basal plus supplemental) is not as reliable as that based on the basal blood pressure alone.

ship between the basal diastolic pressure and prognosis is shown in Figure XII 4b.

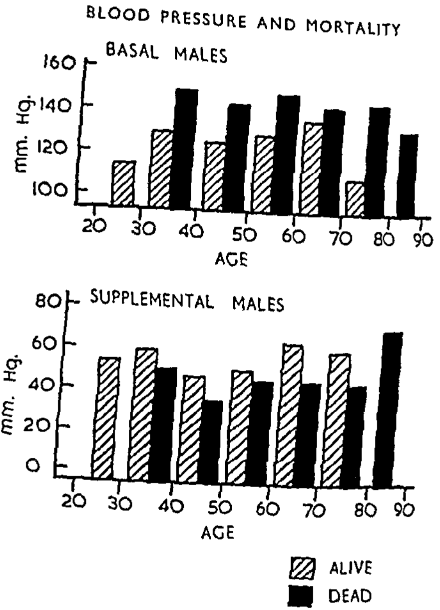



Fig. XII 3b

A comparison is made of the mean basal blood pressures (systolic + diastolic)/2, in males, of 42 patients who survived and of 73 patients who failed to survive 5 years after the measurement It is seen that the average of the mean basal blood pressures was higher in the patients who died

In contrast the average of the mean supplemental blood pressures (systolic + diastolic /2 is less in the patients who died

Even in treated cases we find that the outlook is appreciably worse in those patients who before starting treatment had unusually high basal blood pressures.

It emerges, therefore, that when in the course of clinical routine a

1949) shows beyond doubt that the outlook of hypertension patients who have suffered a 7-day incapacity in the year of study is much worse than of patients who have suffered no such incapacity (Table XII 9).

TABLE XII 9. *Percentage of hypertension cases which were fatal in the year of study (based on household surveys involving 2,500,000 persons in 83 cities and towns and 18 States of U.S.A.).*
(Collins, S. D. Publ. Hlth Rep. (Wash), 64: 1439, 1949)

| | | All ages | Under 20 | 20—44 | 45—64 | 65 and over |
|---|---|---|---|---|---|---|
| All cases | Male | 15.2 | 15.5 | 4.7 | 12.1 | 23.3 |
| | Female | 7.1 | 8.8 | 1.9 | 4.4 | 13.8 |
| Cases who were disabled for 7 or more days | Male | 38.3 | 27.4 | 24.1 | 33.5 | 45.1 |
| | Female | 27.3 | 23.5 | 11.6 | 19.8 | 38.3 |

Keith, Woolf and Gilchrist (1949) conclude that the death rate for persons whose symptoms of so-called benign hypertension lead them to seek help in the hospital is about five times that prevailing in the population as a whole.

## Effect of Retinal Grading

The widespread use of the four retinal grades (Chapter V) as indications of prognosis has consistently confirmed the validity of the observations of Keith, Wagener and Barker (1939). The graph (Figure XII 5) is reproduced from their publication.

Palmer et al. (1948) also stress the grave si[illegible] retinopathy They point o[illegible] or more years of benign [illegible] appeared but, in general, their course has been brief. Perera (1951) found that, in the presence of papilloedema, the average outlook was one year and was five years with grade 3 changes. Most authors do not think there is so great a difference as this between grade 3 and 4 cases. The outlook as well as the retinal appearances, are greatly altered by effective treatment.

## Effect of the Development of Malignant Hypertension

There is sometimes confusion between clinically diagnosed malignant hypertension and malignant hypertension diagnosed histologically But it is not to be expected that papilloedema, which we may regard as a clinical sign of advanced [illegible] with other signs o[illegible] medial necrosis or [illegible]

## EFFECT OF THE PRESENCE OF CLINICAL MANIFESTATIONS

Several authors have commented on the difference between the prognosis of patients with hypertension who are not complaining of symptoms and those who are. Frant and Groen (1950) found 34.6 per cent of deaths in a series of 130 men with symptoms and 6.6 per cent

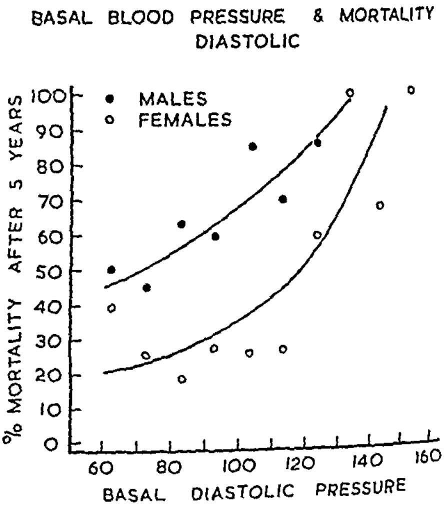



Fig. XII 4b

Relationship between mean basal diastolic pressure and the percentage mortality after 5 years It will be seen that at a given level of the mean basal diastolic blood pressure the percentage mortality is higher in males than in females

in a short series without symptoms. Among 205 women there were 25.8 per cent of deaths in the series with symptoms and 17.6 in those without. The results of Ehrström (1946) suggest that, whereas hypertension is often present for as long as twenty years, the average duration of life after the first subjective symptoms is ten years.

The statistical survey of the U.S.A. Public Health Service (Collins,

1949) shows beyond doubt that the outlook of hypertension patients who have suffered a 7-day incapacity in the year of study is much worse than of patients who have suffered no such incapacity (Table XII 9).

TABLE XII 9. *Percentage of hypertension cases which were fatal in the year of study (based on household surveys involving 2,500,000 persons in 83 cities and towns and 18 States of U.S.A.).*

(Collins, S. D. Publ. Hlth Rep. (Wash), 64: 1430, 1949)

| | | All ages | Under 20 | 20—44 | 45—64 | 65 and over |
|---|---|---|---|---|---|---|
| All cases | Male | 15.2 | 15.5 | 4.7 | 12.1 | 23.3 |
| | Female | 7 1 | 8.8 | 1.9 | 4.4 | 13.8 |
| Cases who were disabled for 7 or more days | Male | 38.3 | 27.4 | 24.1 | 33.5 | 45.1 |
| | Female | 27.3 | 23.5 | 11.6 | 19 9 | 38.3 |

Keith, Woolf and Gilchrist (1949) conclude that the death rate for persons whose symptoms of so-called benign hypertension lead them to seek help in the hospital is about five times that prevailing in the population as a whole.

## Effect of Retinal Grading

The widespread use of the four retinal grades (Chapter V) as indications of prognosis has consistently confirmed the validity of the observations of Keith, Wagener and Barker (1939). The graph (Figure XII 5) is reproduced from their publication

Palmer et al (1948) also stress the [illegible] malignant phase [illegible], in general, their course has been brief. Perera (1951) found that, in the presence of papilloedema, the average outlook was one year and was five years with grade 3 changes. Most authors do not think there is so great a difference as this between grade 3 and 4 cases The outlook as well as the retinal appearances, are greatly altered by effective treatment.

## Effect of the Development of Malignant Hypertension

There is sometimes confusion between clinically diagnosed malignant hypertension and malignant hypertension diagnosed histologically. But it is not to be expected that papilloedema, which we may regard as a clinical sign of advanced disease, will always correspond with other signs of advanced disease, namely, an autopsy finding of medial necrosis or endothelial hyperplasia.

Papilloedema is an ominous sign, as is seen from the high mortality of the grade 4 patients (Figure XII 5). Some grade 3, and even grade 2, cases have a worse outlook than some cases with papilloedema, but as a group the outlook of group 4, in the absence of treatment, is gloomy; and by the time they die most of them show medial necrosis histologically.

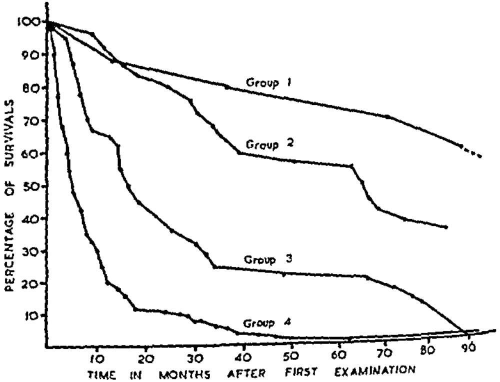



Fig XII 6

Percentage of patients without definitive treatment who survived at various times intervals after the first examination The patients are subdivided into four retinal grades (Keith, N M., Wagener, H P, and Barker, N W Amer. J. med. Sci, 197 : 332, 1930).

The restriction of the term malignant hypertension to patients with papilloedema has the advantage that the patients referred to form a coherent group. So long as papilloedema is regarded as essential for diagnosis the classification is objective and indeed global If the term malignant hypertension comes to be used to denote all kinds of hypertensive patients who are thought to have a very bad prognosis, the term may as well be discarded.

## Effect of Nitrogen Retention and other Renal Abnormalities

The outlook of untreated cases of malignant hypertension is influenced by the presence or absence of normal renal function; in cases on effective hypotensive therapy the renal function is of overwhelming importance in prognosis. Schottstaedt and Sokolow (1953) in a most

valuable article on malignant hypertension noted the less unfavourable course of patients whose renal function was satisfactory. They found, however, that impairment of renal function might develop in as short a time as one week and uraemia in six months from the time of diagnosis. Twelve patients out of 37 with good renal function survived eighteen months, thirteen having some form of therapy such as sympathectomy or low sodium diet. Nine out of 37 survived thirty months and 6 out of 13 of these cases either had a sympathectomy or a salt restricted régime. Among the 67 cases without evidence of good renal function none survived ten months.

Even when there is no malignant hypertension almost all authors regard impairment of concentrating capacity, or a significant degree of nitrogen retention as indicative of a poor outlook. If the total non-protein nitrogen in blood exceeds 50 mg. per cent the outlook is usually poor — a matter of a year or so unless the retention of nitrogen is due to congestive heart failure or to a disturbance in water balance or to prostatic obstruction. Perera (1951) found the outlook to be about one year when nitrogen retention was present.

Persistent albuminuria seems to worsen the prognosis of hypertension (Griep et al., 1951). Albumin with casts is unsatisfactory from the standpoint of life insurance, the mortality being in the region of 161 per cent of the expected. The presence of associated hypertension makes the outlook even less favourable. Christiernin et al. (1939) find even moderate hypertension with albumin and casts warrants a substantial adverse rating.

### Effect of a Cerebral Vascular Accident

[illegible]

va [illegible]

[illegible] years, which was a shorter life expectancy than most of his cases. Blackford et al. (1930) found the proportion of deaths which occur from cerebral haemorrhage was greater in cases with very high blood pressures than in cases with moderate elevation. Some patients, however, live for many years after a stroke, especially when the disability is moderate. Many of these strokes are presumably due to cerebral thrombosis.

When cerebral haemorrhage, as distinct from subarachnoid haemorrhage, complicates hypertension death usually takes place within a few days though sometimes death is delayed for a few weeks[5, 32, 61].

### Effect of the Presence of Heart Failure and Cardiac Asthma

The outlook for hypertensive heart failure patients treated for the heart failure but not receiving hypotensive therapy is between a few

months and five years, usually about two years. Rapid recovery on such treatment suggests the longer outlook, and continued breathlessness at rest that the end is near. Goldring and Chasis (1944) found an average life duration of 1.8 years from the first evidence of heart failure. The great relief which is consistently obtained by the use of hypotensive agents is referred to elsewhere (Chapter XIX).

### Effect of Angina and Cardiac Infarctions

The presence of these complications usually worsens the prognosis appreciably. In mild or moderate hypertension the outlook may be five or more years in untreated cases.

### Effect of Cardiac Enlargement

Cardiac hypertrophy is associated with a diminished life expectancy[57], the curtailment of life being the greater as the heart enlarges further (Perera, 1951).

Rasmussen and Bøe (1945) found the deaths in six years rise from 32 per cent in patients with normal or near-normal heart size to 80 per cent in those with gross cardiac enlargement, and the proportion of cardiac deaths increased.

### Effect of Electrocardiographic Abnormalities

Perera (1951) found that the average duration of hypertensive disease in 100 patients was nineteen years, but it was only seven years in those with electrocardiographic abnormalities suggesting myocardial damage.

The electrocardiographic abnormalities commonly encountered in hypertension (Chapter V) may be either secondary to the hypertension or due to associated coronary disease or other forms of myocardial damage. Early electrocardiographic signs of hypertension, such as increased height of the R wave, and flattening or slight inversion of the T wave in leads reflecting left ventricular potentials (Lead I, $aV_L$ and V5 and 6), are earlier signs than radiographic heart enlargement and are probably associated in most instances with concentric hypertrophy of the left ventricular wall. The more advanced changes are usually encountered with more substantial degrees of hypertension. I agree with the many authors who find the presence of electrocardiographic abnormalities worsens the outlook of the untreated case [12, 17, 41, 43]. My impression is that evidence of myocardial disease is more important for prognosis than early hypertensive changes.

Flaxman (1944) and Ranges (1949) were not impressed with the prognostic [illegible] of electrocardiograms in hypertension Rasmussen and Bøe (1945) [illegible] cases followed for an average of six years that [illegible] cardiograms died and the percentage of deaths increased to 73 per cent and 100 per cent respectively in the two most advanced

categories. The proportion of cardiac deaths also increased. Daley et al (1943) studied 426 symptomless life insurance applicants with hypertension. The ratio of actual to expected mortality was as follows·

| | |
|---|---|
| Normal electrocardiogram | 181 per cent |
| Borderline electrocardiogram | 269 per cent |
| Left ventricular hypertrophy pattern | 344 per cent |
| Evidence of myocardial disease | 375 per cent. |

## References


1 Actuarial Society of America and the Association of Life Insurance Medical Directors. Blood Pressure. Report of the Joint Committee on Mortality, 1925

2 Actuarial Society of America and the Association of Life Insurance Medical Directors [illegible]

3 [illegible] Directors Blood Pressure Study, 1939

4 Actuarial Society of America and the Association of Life Insurance Medical Directors Supplement to Blood Pressure Study, 1941.

5 ARING, C [illegible] hem [illegible] stuc [illegible]

6 BECHGAARD, P. Arterial hypertension — Follow-up study of 1000 hypertonics Acta med scand, suppl. 172 1946.

7 BECHGAARD, P, KOPP, H., and NIELSEN, J One thousand hypertension patients followed from 16—22 years International Congress of Medicine, Stockholm, September, 1954

8 BLACKFORD, J. M., BOWERS, J M, and BAKER, J W Follow-up study of hypertension. J Amer med Ass, 94. 328, 1930

9 BURGESS, A. M. Excessive hypertension of long duration N Engl. J. Med, 239· 75, 1948.

10 [illegible]

11 [illegible] heart disease V. Illness from heart and other cardiovascular-renal diseases in general morbidity surveys of families Publ. Hlth Rep (Wash), 64: 1439, 1949

12 DALEY, R. M, UNGERLEIDER, H E, and GUBNER, R S. Prognosis in hypertension J Amer. med Ass, 121. 383, 1943

13 DIEHL, H S, and HESDORFFER, M B Changes in blood pressure of young men over a seven year period Arch intern Med., 52: 948, 1933

14 DROLLER, H, PEMBERTON, J., ROSEMAN, C, and GROUT, J. L. A High blood pressure in the elderly. Brit med [illegible]

15 DUBLIN, L [illegible] recent [illegible] Amer, [illegible]

16 EHRSTRÖM, [illegible] die Prognose der essentiellen Hypertonie. Klin Wschr., 5 469, 1926

17 FILLEY, G F The clinical significance of certain changes in the limb lead electrocardiogram in arterial hypertension Bull. Johns Hopk. Hosp., 79. 281, 1946

18 FISHBERG, A. M Hypertension and Nephritis. Lea and Febiger, Philadelphia, 1954

19 FLAXMAN, N. The treatment of hypertension — Comparison of mortality in medically and surgically treated cases. Ann intern. Med, 20 120, 1944.
20 FRANT, R., and GROEN, J. Prognosis of vascular hypertension Arch. intern Med., 85: 727, 1950.
21 FROST, H. M. Hypertension and longevity. Life Insurance Med, 1: 178, 1926.
22 GOLDRING, W., and CHASIS, H. Hypertension and hypertensive disease. The Commonwealth Fund, New York, 1944.
23 GOVER, M Physical impairments of members of low-income farm families — 11,490 persons in 2,477 rural families examined by the Farm Security Administration, 1940. VII. Publ. Hth. Rep (Wash.), 63: 1083, 1948
24 GRIEP, A. H, BARRY, G. R., HALL, W. C., and HOOBLER, S. W The prognosis in arterial hypertension — Report on 117 patients under 53 years of age followed 8 to 10 years. Amer. J. med. Sci, 221: 239, 1951
25 HAMMARSTRÖM, S., and BECHGAARD, P. Prognosis in arterial hypertension — Comparison between 251 patients after sympathectomy and a selected series of 435 non-operated patients. Amer. J. Med., 8: 53, 1950
26 HINES, E. A. Jr. Range of normal pressure and subsequent development of hypertension; follow-up study of 1,522 patients. J. Amer. med Ass, 115: 271, 1940
27 HUNTER, A. Blood pressure among standard lives. J. Inst. Actuaries, 70 60, 1939.
28 International Congress on Life Assurance Medicine, London, 1935
29 JANEWAY, T C A clinical study of hypertensive cardiovascular disease Arch intern Med, 12: 755, 1913
30 KEITH, M. A, WOOLF, B., and GILCHRIST, A. R. Results of medical and surgical treatment of essential hypertension Brit. Heart J., 11: 287, 1949
31 KEITH, N. M, WAGENER, H P., and BARKER, N. W. Some different types of essential hypertension. Their course and prognosis Amer. J. med. Sci, 197: 332, 1939
32 KING, R L, CARLILE, T, and BLACKFORD, J M. Hypertension, follow-up study of 481 patients Northw. Med. (Seattle), 41: 298, 1942
33 LEISHMAN, A. W D Observations on prognosis in hypertension Brit. med J, 1. 1131, 1953
34 LEVY, R. L, WHITE, P D, STROUD, W. D., and HILLMAN, C. C Transient hypertension — The relative prognostic importance of various systolic and diastolic levels. J Amer. med. Ass, 128: 1059, 1945a.
35 LEVY, R L, WHITE, P D, STROUD, W D., and HILLMAN, C. C. Transient tachycardia — Prognostic significance alone and in association with transient hypertension. J Amer med Ass, 129: 585, 1945b
36 LEVY, R L, WHITE, P D, STROUD, W. D., and HILLMAN, C C. Sustained hypertension — Predisposing factors and causes of disability and death J Amer med Ass, 135: 77, 1947.
37 MACKENZIE, L F., and SHEPHERD, P. Significance of past hypertension in applicants later presenting normal average pressure. Proc. A. Life Insur M Dir America (1937), 24: 157, 1938 Cited by Levy, R L., White, P D., Stroud, W D., and Hillman, C C J Amer med Ass, 128. 1059, 1945.
38 MASTER, A. M. Cardiovascular problems in war; hypertension and the navy. Bull N. Y. Acad Med., 19: 704, 1943.
39 MAY, O. Mortality in relation to hyperpiesia. Brit. med. J, 2: 1166, 1925
40 MONROE, R T Diseases in old age. Harvard University Press, Cambridge, 1951.

41 Oppenheimer, B. S., and Rothschild, M. A. The value of the electrocardiogram in the diagnosis and prognosis of myocardial disease Trans. Ass. Amer. Phys, 39: 247, 1924

42 Palmer, R. S The significance of essential hypertension in young male adults. J. Amer. med. Ass, 94: 694, 1930.

43 [illegible]

44 Palmer, R. S, and Muench, H. Course and prognosis of essential hypertension: Follow-up of 453 patients ten years after original series was closed. J. Amer. med Ass, 153: 1, 1953.

45 Paullin, J. E Ultimate results of essential hypertension. J. Amer. med. Ass, 87: 925, 1926.

46 Perera, G A The life history of one hundred patients with hypertensive vascular disease. Amer. Heart J., 42: 421, 1951.

47 Pickering, G. W. High blood pressure. J. & A. Churchill Ltd, London. 1955

48 Ranges, H A. Benign aspects of hypertensive disease — A group study. Med Clin. N. Amer., 33: 611, 1949

49 Rasmussen, H., and Bøe, J. The prognosis of essential hypertension, with remarks respecting the indications for operative treatment Acta med. scand, 120: 12, 1945

50 Robinson, S. C Hypotension: The ideal normal blood pressure. New Engl. J. Med, 223: 407, 1940

51 Robinson, S C., and Brucer, M Range of normal pressure statistical [illegible]

52 [illegible]

53 Russek, H I Blood pressure in the aged — A study of one thousand elderly male subjects Amer. Heart J, 26: 11, 1943.

54 Schottstaedt, M F., and Sokolow, M The natural history and course of hypertension with papilledema (malignant hypertension) Amer Heart J, 45 331, 1953

55 Stieglitz, E. J. Emotional hypertension Amer. J. med. Sci, 179: 775, 1930

56 Symonds, B The blood pressure of healthy men and women. J. Amer. med Ass., 80. 232, 1923

57 von Monakow, P. Blutdrucksteigerung und Niere Dtsch Arch klin. Med, 133 129, 1920.

58 Weitz, W, and Sieben, A Beitrag zur Prognose der essentiellen Hypertension Münch. med. Wschr, 73 2197, 1926

59 Wood, P. H Diseases of the heart and circulation Eyre and Spottiswoode, London, 1950

60 Woolsey, T D. Statistical studies of heart disease VI. Age at onset of heart and other cardiovascular-renal diseases Publ Hlth. Rep. (Wash.), 65 555, 1950

61 Zimmerman, H M Cerebral apoplexy; mechanism and differential diagnosis N Y St J Med, 49 2153, 1949

CHAPTER XIII

# SOME FUNDAMENTAL PRINCIPLES CONCERNING THE TREATMENT OF HYPERTENSION BY BLOOD PRESSURE REDUCTION

## FUNDAMENTAL PRINCIPLES

*Reduction of the blood pressure is not directed to removal of basic causes; but effective blood pressure reduction breaks a link in the chain of causation.* Essential hypertension is both a syndrome and a disease. *It is a syndrome in that its characteristic clinical and pathological features form part of all protracted high blood pressure cases, whatever the primary cause. It is a disease in that, in the clinical condition we call essential hypertension, the syndrome is the whole disorder.* In nephritis, cortical hyperadrenalism, and many other conditions associated with blood pressure elevation, the syndrome of essential hypertension is only part of the disease.

*In essential hypertension, whatever underlying primary causes are responsible for high blood pressure, they are, in themselves, unproductive of symptoms.* The clinical manifestations of the disorder are secondary to the arterial hypertension (or associated vasoconstriction). *Indeed, it seems to me, that as the blood pressure rises to levels which may lead to secondary manifestations we are witnessing the gradual emergence of a disorder: the transition from physiological variants and symptomless pathology to a recognizable abnormality which may cause disability or death.*

There is now, I believe, conclusive evidence that blood pressure reduction of sufficient degree and duration may be relied upon to disperse, or relieve greatly, the reversible clinical manifestations which are secondary to hypertension. Holding these views the author regards effective blood pressure reduction (with relief of excessive vasoconstriction) as a fundamental and not as a secondary object in treatment.

There are differences of opinion on many important issues: which patients are severe enough to be treated and which may be properly left without definitive therapy, by which agencies should blood pressure reduction be effected, and to what extent should the blood pressure be reduced in particular cases. These matters of detail should not obscure the main issue, namely, that blood pressure reduction may prolong

life, relieve severe hypertensive manifestations, lead to objective improvements and enable patients to increase their activity and lead more productive lives. Those who are satisfied to ameliorate invalidism while waiting for drugs which are easier to use, may find the desired improvements arrive too late for some patients.

In the author's view a variety of surgical procedures, severe salt restriction and several drugs may be successful, on occasion, in eliciting effective reductions of the blood pressure in hypertensive patients. It is generally agreed that ganglion blocking drugs with the help of posture are the most potent and certain of hypotensive agencies, but there are technical difficulties in their use. Rauwolfia alkaloids almost always make it possible to retain control of the blood pressure on reduced doses of ganglion blocking drugs, and an adequate hypotensive régime, though it may be difficult to achieve, can usually be made comfortable for the patient. [illegible] alkaloic [illegible] availab [illegible] unsatisfactory in doses sufficient to induce adequate falls of blood pressure. There are several ways in which misconceptions may arise concerning the actions of hypotensive or allegedly hypotensive drugs:

1. Administration of placebos with *repeated visits to the doctor*, and establishment of confidence, often induces symptomatic improvement and falls of blood pressure to near normal levels. This occurs in patients whose casual blood pressures are elevated but whose basal blood pressures are low. Such patients seldom require treatment, although their progress should be followed.

2. It is sometimes overlooked that the administration of active drugs in placebo doses are just as effective as genuine placebos in reducing the blood pressure in these patients, and symptomatic benefits may be recorded I think some of the results claimed for veratrum alkaloids, administered in sub-emetic doses, have been obtained in this way.

It is therefore important to ascertain if a drug which is to be taken for many years is having something more than a placebo action. In our clinic we have had the help of a technician service, and in respect of drug therapy the conclusions we have reached are based on a clinical study, including the results of over 16 000 [illegible] active dr[illegible] fc [illegible] p[illegible]

[illegible] problem is whether [illegible] hype[illegible]

[illegible] fundamental issues:

[illegible] possible to *prevent the development of some or many hypertensive manifestations?* It has been stated that many years must elapse

CHAPTER XIII

# SOME FUNDAMENTAL PRINCIPLES CONCERNING THE TREATMENT OF HYPERTENSION BY BLOOD PRESSURE REDUCTION

## FUNDAMENTAL PRINCIPLES

Reduction of the blood pressure is not directed to removal of basic causes; but effective blood pressure reduction breaks a link in the chain of causation. Essential hypertension is both a syndrome and a disease. It is a syndrome in that its characteristic clinical and pathological features form part of all protracted high blood pressure cases, whatever the primary cause. It is a disease in that, in the clinical condition we call essential hypertension, the syndrome is the whole disorder. In nephritis, cortical hyperadrenalism, and many other conditions associated with blood pressure elevation, the syndrome of essential hypertension is only part of the disease.

In essential hypertension, whatever underlying primary causes are responsible for high blood pressure, they are, in themselves, unproductive of symptoms. The clinical manifestations of the disorder are secondary to the arterial hypertension (or associated vasoconstriction). Indeed, it seems to me, that as the blood pressure rises to levels which may lead to secondary manifestations we are witnessing the gradual emergence of a disorder: the transition from physiological variants and symptomless pathology to a recognizable abnormality which may cause disability or death.

There is now, I believe, conclusive evidence that blood pressure reduction of sufficient degree and duration may be relied upon to disperse, or relieve greatly, the reversible clinical manifestations which are secondary to hypertension. Holding these views the author regards effective blood pressure reduction (with relief of excessive vasoconstriction) as a fundamental and not as a secondary object in treatment.

There are differences of opinion on many important issues: which patients are severe enough to be treated and which may be properly left without definitive therapy, by which agencies should blood pressure reduction be effected, and to what extent should the blood pressure be reduced in particular cases. These matters of detail should not obscure the main issue, namely, that blood pressure reduction may prolong

d may be found to be useful, either alone or in combination. The know-edge which their study has brought to the subject of therapy remains of more than historical interest.

## MANAGEMENT AND SIMPLE THERAPEUTIC MEASURES

Several chapters have been concerned with subject matter relating to the clinical investigation of hypertensive patients. A list of the main topics may be convenient for reference.

### Clinical Investigations

Aspects of a routine investigation which deserve special attention are set out in a copy of the record form used in the Dunedin Hospital hypertensive clinic (Appendix 4). An account of the clinical manifestations and complications to which hypertensive patients are liable is given in Chapter V. The study of aetiology and certain special investigations which may be relevant are in Chapter VI. Psychosomatic problems are referred to in Chapter VII.

The basal blood pressure is of the first importance, and an account of a hospital technique is given in Chapter II and of equally satisfactory technique for general practice in Appendix 5. The relation to prognosis is summarized in Chapter XII. Renal function tests should be performed [illegible] ... starts, if only as a reference standard for assessment of progress. In special cases pyelographic studies and tests for phaeochromocytoma are made. Biopsy samples may be required if periarteritis nodosa is suspected and endocrine studies are appropriate in some cases.

### Clinic Organization

Reference to a type of clinic organization is given in Appendix 6.

### Advice to Patients

It will be decided by clinical investigation, including basal blood pressures, whether to recommend effective hypotensive therapy or whether simple measures will suffice, and of these the most important is reassurance based on clinical evidence.

The question of whether a patient should be told if the blood pressure is overaverage or not, may be decided in terms of the patient's personality, the expectation of their acquiring the information elsewhere, and upon the future course of action upon which the physician has decided. My own practice, when blood pressures are moderately elevated, is to inform suitable patients about the blood pressure in

before the results of hypotensive therapy can be assessed in respect of the possibility of preventing disorders secondary to hypertension. While many problems require several more years for their solution, some direct evidence and much circumstantial evidence is available now. Evidence from our clinic and others will be referred to later which, we believe, shows the incidence of heart failure and cardiac asthma to be much reduced in severe hypertensive patients on treatment with ganglion blocking drugs, and the incidence of cerebral vascular accidents to have been reduced since more effective means of reducing the blood pressure became available, using newer ganglion blocking drugs in combination with Rauwolfia alkaloids. Some theoretical reasons will be given also for believing that hypertensive manifestations can be prevented.

2. *Assuming that some hypertensive manifestations can be prevented by reducing the blood pressure, is it possible to decide which patients have a sufficiently high expectation of a cerebral vascular accident or other important disability to warrant the institution of treatment before symptoms or serious objective manifestations arise?* Precise individual forecasts cannot be made but it is the view of our clinic that a useful indication of the expectation of the disability from hypertension can be obtained by the clinical study of patients.

The follow-up studies on a series of untreated hypertensive patients who had basal blood pressures done between 1946 and 1950 have convinced us that basal blood pressures are more valuable as a guide to prognosis and the need for treatment than are casual blood pressures; and that our policy for the future should be to treat some of the symptomless hypertensives whose basal blood pressures are high because, as a group, their outlook untreated is poor. Casual blood pressure readings are deceptive for they place in the same category patients whose blood pressure is comparatively low away from the clinic environment with those whose pressures are constantly high. Their prognosis is very different. It is true that many patients, especially women, whose casual blood pressures are very high may live 15 or 20 years without developing important symptoms or serious hypertensive manifestations. It is also true that many of them with high basal blood pressures die within a few years.

The preliminary investigation and therapy of hypertension requires a meticulous attention to detail, but thereby better results are obtained, including improvements in the comforts of patients and the avoidance of unnecessary alarm.

Where opinions concerning therapy diverge I have endeavoured, in what follows, to give a representative account of these. Indeed, much space has been given to the consideration of surgical procedures, and drugs for which I find no use at the present time. But the subject is developing so rapidly that drugs related to those which seem to be discard-

patients should attempt to avoid tenseness and develop a more relaxed habit of mind. Although some patients cannot avoid tenseness, some appreciate that effective work may be accomplished without it, and that cultivation of mental and muscular relaxation may successfully lessen this symptom. The use of phenobarbitone may help (½ gr. thrice daily, or even a little more at first).

It is my impression that elaborate or protracted forms of psychotherapy have no special place in hypertension. [illegible]

pressure. [illegible]

hypertension, it will be the physician's task to decide if the patient's happiness, health, activity and future prospects are best served by "masterly" inactivity, a change in the patient's way of life, or drug therapy aimed at a return of the blood pressure to a near-normal level.

### Obesity

Reference has been made in Chapter III to the relationship between obesity and the level of the blood pressure. There seems little doubt that reduction in overweight is desirable. Aside from hypertension, obesity is associated with a higher incidence of cardiovascular disorders and with a decreased life expectancy. It is usually worthwhile apart from any effect upon the blood pressure level.

No set diet is suitable for all patients. Where income permits it we advise patients to gain a large proportion of their calories from lean meat, salads and green vegetables, reducing the fat intake to the lowest limit of palatability. In countries such as New Zealand and Australia where butter is consumed in large quantities, we advise patients to cut out this article of diet to a large extent, having, for example, toast and marmalade for breakfast with no butter and to remove the fat from meat. In patients who return frequently to the clinic, repeated weighings are perhaps the most valuable therapeutic procedure. Where diets are very low in calories, we advise the use of vitamin supplements.

### Sedatives

Phenobarbitone is not infrequently advised for patients who are unduly tense and a sedative at night for those who do not sleep well. Certainly some symptoms occurring in moderate or mild hypertensive patients are removed in this way. Whether the symptoms are due to the hypertension is another matter. Of recent years Rauwolfia alka-

general terms; for example that it is near the upper limits of normal; is slightly but not dangerously high; that a periodic examination is required but drug treatment would be superfluous at the present time. A brief medical interview with a blood pressure measurement, possibly other investigations also, may be arranged at intervals of 6, 12 or 24 months, depending on the circumstances.

Information concerning the basal blood pressure provides potent and valid reassurance in certain cases. For example, a patient who has been informed already that the (casual) blood pressure is very high, and whose basal blood pressure is found to be at a low level, can be faithfully assured that the test has shown that much of the blood pressure elevation is a reaction to the doctor and his consulting room; that this is a physiological reaction and not an indication of neuroticism; that during sleep the blood pressure is near to normal; that there is nothing particularly ominous about the figure 200 which may occur in health during violent exercise. Patients are assured that, if treatment becomes necessary, means are now available for reducing the blood pressure.

Some physicians advise patients to change their way of life, and go slowly. This is a highly individual matter and general advice which fails to take account of the background, hopes, fears, needs, and aims of the patient is unlikely to be beneficial. Personal advice may warrant several consultations. If it has been decided that active treatment is unnecessary then advice should aim at:

1. Relief of unnecessary anxiety and strain.
2. Assisting the patient to enjoy as productive and active a life as age permits.

These objects are rarely achieved by advising: retirement, change of occupation, celibacy, no parties, no cinema, no alcohol, no tobacco, no meat, no salt, no spicy food, no lively interests, bed at 9 p.m. and for pleasure a therapeutic walk at a measured pace. The avoidance of excesses is another matter.

3. If hypertension or manifestations secondary to it make it necessary to curtail work or reasonable enjoyment, the question of whether a pharmacological method of controlling the blood pressure would be preferable should be re-examined.

Diminution in the stress and strain of living is an advantage to hypertensive patients which need not interfere with their happiness or with normal productivity. Those who drive themselves overmuch, who live at too high a pressure, may be given appropriate advice; but it is seldom necessary to reduce hours of work below the normal, or in the case of people carrying heavy responsibility to abandon this and their ambitions of service or personal advancement. Frustration and loss of interest may be more harmful than a little overwork. Hypertensive

CHAPTER XIV

# SURGICAL TREATMENT OF HIGH BLOOD PRESSURE

Divergent conclusions have been drawn concerning the extent of the benefits to be derived from surgery. There is, however, a consensus of opinion that in selected cases the results of surgery are better than the results of palliative treatment. It is the author's view that the results of the more adequate methods of medical treatment available in recent years are better than those claimed for surgery, at least in the more severe cases; but to obtain good results consistently seems to require a specialized knowledge of the subject

In our Dunedin hospital no sympathectomy has been performed for high blood pressure during the last four or five years and to the best of my knowledge no surgeon attached to our hospital has performed a sympathectomy for hypertension in his private practice. Other surgeons also regard the operation as superceded (Trumble, 1954). But while the use of surgical treatment seems to have diminished in most countries it has b...
surgery, or
most satis ... patients (...wick and Thompson, 1953; D'Abreu, 1953).

It seems desirable first to make clear and examine the views of those who regard surgical procedures as the preferred methods of treatment.

## SELECTION OF PATIENTS FOR SYMPATHECTOMY

A comparison of the results of surgery with those of the various forms of palliative medical treatment available before 1950, presents difficulties of which the most important is that of obtaining comparable groups of patients

A surgeon is constrained *to select patients* who are likely to withstand the operation and who have *expectations of show...*
Recommendat...

On reporting the results of their pioneer studies Allen and Adson

loids have come to be used for such mild cases as a substitute for phenobarbitone. With these drugs there is a risk of the occurrence of mental depression, at least with daily doses of 0.75 mg. or more of reserpine. But the calming effect of Rauwolfia alkaloids has been of immeasurable benefit to some patients.

At the present time, when sedation is the aim, I do not regard Rauwolfia alkaloids as a reasonable substitute for phenobarbitone.

| Authors | Manifestations which discourage operation |
|---|---|
| Harland & D'Abreu, 1949 | Auricular fibrillation, congestive heart failure, past or present, and evidence of coronary artery disease are contraindications to operation. Patients with considerable cardiac enlargement, persistent pulsus alternans, gallop rhythm or gross E.C.G. changes are unlikely to improve and should be submitted to operation only when other strong indications are present. |
| Glaser, 1950 | Renal disease with insufficiency. Serious cerebral impairments and sometimes cardiac impairments. |
| Hoobler et al., 1951 | Patients with elevated non-protein nitrogen should not be treated surgically. |
| Chris, 1951 | The patient must not be in cardiac or renal failure. If there has been a cerebral vascular accident the patient must have recovered without important residues. The diastolic blood pressure should respond to rest or sedation by a fall of at least 20 mm |
| McGavin, 1952 | [illegible] cardiac or cerebral vascular accidents, severe heart failure not responding to medical treatment and severe angina. |
| Hantschmann, 1953 | Severe heart impairments, substantial renal or brain damage. |
| Thompson and Smithwick, 1953 | The one positive contraindication to splanchnicectomy is severe kidney damage as indicated by persistent evidence of nitrogen retention. |
| Vons, 1955 | Cardiac failure or serious impairment of renal function contraindicate operation. Unless drops of 20 mm. or more in the diastolic pressure occur with sodium amytal the patient will be unlikely to have a good result. |

(1938) concluded — "It is useless to operate on patients who have any *significant* renal insufficiency, congestive heart failure, angina pectoris or a cerebral vascular accident from which recovery has not been satisfactory." Most surgeons now hold different views about the selection of patients, but it is clear that Allen and Adson were only prepared to recommend the operation in comparatively mild cases and their recommendations were followed for many years by other surgeons.

Some examples of types of cases in which the authors mentioned do not recommend surgery are set out in the following table:

| Authors | Manifestations which discourage operation |
|---|---|
| Bridges & White, 1947 | Non-protein nitrogen over 50 mg. per cent. Diastolic blood pressure fails to drop to 110 or lower with sodium amytal. |
| Dickson Wright, 1947 | Severe renal damage, severe heart damage, pulsus alternans, more than minor residual damage after cerebral vascular accident. A low blood pressure on sedation was an indication to operate. |
| DeTakats, Julian & Fowler, *1948* | Extensive damage to brain, retina, heart or kidney is a contraindication, but a previous stroke or coronary occlusion is not by itself a contraindication if the rest of the organs are satisfactory. Persistent papilloedema and nitrogen retention are absolute contraindications. |
| Ray, 1949 | Patients with serious functional damage of the brain, heart or kidneys are excluded. Patients with appreciable encephalopathy or multiple vascular accidents are excluded. Heart block, heart decompensation, or fibrillation that does not respond promptly to digitalis and coronary occlusion are contraindications. |
| Craig, 1949 | Irreversible changes in the vascular, muscular and nervous systems as well as in the heart, kidneys and other vital organs, indicate a condition not amenable to operation |

*Numerical Value of Various Factors that Influence Prognosis*
(Smithwick, R. H. J. Amer. med. Ass., 147: 1611, 1951)

| | Numerical Value of each Factor |
|---|---|
| Cerebrovascular accident with or without minor residue<br>Abnormal electrocardiogram<br>Enlarged heart<br>Impending congestive failure<br>Phenolsulfonphthalein excretion, less than 25 % in 15 min or less than 60 % in 2 hr.<br>Age 50 or over<br>Mild angina | 1 |
| Cerebrovascular accident, with residual defects<br>Frank congestive failure, moderate angina<br>Phenolsulfonphthalein excretion, less than 20 % in 15 min<br>Unsatisfactory response to sedation | 2 |
| Phenolsulfonphthalein excretion, less than 15 % in 15 min | 3 |
| Nitrogen retention | 4 |

Example 1

| | |
|---|---|
| Abnormal electrocardiogram . . . . | 1 |
| Cerebrovascular accident without significant residual defect . . . . | 1 |
| Phenolsulfonphthalein excretion, 20 % in 15 min. | 1 |
| Total . . . . | 3 = Numerical grade of patient with hypertension |

Example 2

| | |
|---|---|
| Abnormal electrocardiogram . . . . | 1 |
| Enlarged heart . . . . | 1 |
| Phenolsulfonphthalein excretion, 10 % in 15 min. . | 3 |
| Total . . . . | 5 = Numerical grade of patient with hypertension |

Joly et al. (1955) find that lasting falls of blood pressure are much more frequent in patients under age 40. Most surgeons prefer patients under 50 years but they accept a few between 50 and 60. It is evident that it would be inappropriate to compare the results of surgery in these restricted groups of patients with the results of palliative medical treatment in groups of patients which include the many serious cases which have been referred to in the table as unsuitable for surgery.

Some authors, for example (Ray, 1949; Craig, 1949; Smithwick, 1951; D'Abreu, 1954), have contrasted their surgical results with Keith and Wagener's findings in unselected patients with hypertension. The surgical figures would be less impressive if we were to eliminate from the Keith-Wagener series all the very sick patients who were considered unpromising for surgery. The subdivision of patients for the purpose of comparison into grades is of clinical value but not all patients in such clinical groups are comparably severe. For example, the Keith-Wagener grade 4 includes patients with papilloedema and other retinal signs but no other significant lesion secondary to the high blood pressure. The group also includes patients with papilloedema who are in a late stage of renal failure, or in advanced congestive heart failure, or who have suffered a cerebral vascular accident. If in analysing results of treatment the surgical cases can only be selected from the milder patients of group 4, whereas medical cases are unselected and include both the mild and the severe cases, then a better result for surgery is assured from the outset. Smithwick and Thompson (1953) remarked on the difficulties of using the Keith-Wagener cases as controls and introduced a numerical scoring system which is probably better as an index of severity.

ment. Smithwick's group 4 also includes patients with advanced renal insufficiency and patients with marked residues from cardiovascular accidents and patients with combinations of disabilities which are so advanced that surgical treatment could hardly be contemplated. The classification of patients into the Smithwick or other groups is an important aid to prognosis and to the selection of patients for various forms of treatment but this does not mean that medical and surgical patients belonging to some such group are of comparable severity.

## TYPES OF OPERATIONS

Danielopolu and Pende were apparently the first to suggest a neurosurgical approach to the treatment of hypertension and Rowntree and Adson (1925) were apparently the first to perform sympathectomy for hypertension. The following procedures have been used.

In 1925 Rowntree and Adson described resection of 2, 3 and 4L ganglia with the connecting trunks

In 1927 Pieri used a supradiaphragmatic approach to resect the left splanchnic nerves.

In 1932 Craig and Brown used a subdiaphragmatic approach resecting the greater and lesser splanchnic nerves and the sympathetic trunk between 12D and 1L ganglia inclusive. This was a bilateral operation.

In 1933 Craig and Brown used a supradiaphragmatic approach to resect the greater and lesser splanchnic nerves bilaterally.

In 1934 Adson and Brown introduced an intraspinal operation for section of the anterior nerve roots from 6D to 2L.

In 1935 Peet described bilateral supradiaphragmatic approach, resecting the sympathetic trunk and ganglia from 9 or 10D to 12D inclusive.

In 1936 Adson, Craig and Brown used a bilateral subdiaphragmatic approach to resect the greater and lesser splanchnic nerves together with the ganglia of 1 and 2L. In some instances a partial adrenalectomy was done.

In 1938 Crile undertook coeliac ganglionectomy.

In 1940 Smithwick resected the greater and lesser splanchnic nerves and the sympathetic trunk from 9D to 2L inclusive. Approach was both supra- and infradiaphragmatic.

In 1941 Grimson did a three stage operation with total thoracic and partial to total lumbar sympathectomy and coeliac ganglionectomy.

In 1941 Heuer and Glenn resected the anterior thoracic roots.

In 1946 Hinton and Lord resected D8 to L2 or D3 to L2.

In 1947 Poppen and Lemmon resected the greater and lesser splanchnic nerves and the sympathetic trunk from the 4D to 2L inclusive.

In 1949 Boyd and Monro described a sympathectomy extending

*Classification of Hypertensive Patients*
(Smithwick, R. H. J. Amer. med. Ass., 147: 1611, 1951)

| Group | Numerical Grade | Other Factors |
|---|---|---|
| 1 | Less than 4 | Eyegrounds grade 0 or 1* No changes in cerebral, cardiac, or renal areas |
| 2 | Less than 4 | Eyegrounds grade 0 or 1, with changes in cerebral, cardiac, and/or renal areas Eyegrounds grade 2, 3, or 4 with or without changes in cerebral, cardiac, or renal areas* |
| 3 | 4 or more | *Resting diastolic level below 140 mm. Hg Changes are present in cerebral, cardiac, and/* or renal areas, but they do not include the following: Cerebrovascular accident, with marked residual defects Frank congestive failure Phenolsulfonphthalein excretion, below 15 % *in 15 minutes, associated with a poor response* to sedation |
| 4 | 4 or more | Resting diastolic blood pressure below 140 mm. Hg combined with one or more of the *following*: Cerebrovascular accident, with marked residual defects Frank congestive failure Phenolsulfonphthalein excretion, below 15 % in 15 minutes, combined with a poor response to sedation Patients with a resting diastolic level of 140 mm. Hg or more. |

* Eyegrounds are graded according to the criteria of Keith, Wagener and Barker.

Smithwick considers surgery is the best treatment for patients in groups 2 and 3, but in refractory group 2 and 3 cases diet and drug therapy may have to be added. In group 4 cases surgery may be recommended, if the renal function is adequate and the patient is a satisfactory operative risk; but the eventual mortality is *high in* group 4.

The *difficulty still remains of including patients* with very different prognoses within a single severity grade. For example, in Smithwick's group 3 (which differs from the Keith-Wagener grade 3) the eye ground changes may be of grade 2, 3 or 4, but the outlook for patients with retinal grades 2, 3 and 4 are very different. Smithwick's group 4 includes patients with a resting diastolic level of 140 mm., also *diastolic* pressures above or below 140 mm. Hg combined with frank congestive failure. These two groups of patients are *essentially* amenable to treat-

operative breathlessness. Hillestad (1955) referred to the development of angina on lowering of the blood pressure in some patients. Kahn (1954) mentions chylothorax as a possible complication of sympathectomy.

## CLINICAL RESULTS OF SYMPATHECTOMY

### Physiological Effects

Although the extents of sympathectomy operations differ, the resulting circulatory and other clinical manifestations are of the same kind. Patients show individual differences in the degree to which they are affected by sympathectomy; and also extensive sympathectomies are more likely to induce substantial changes in autonomic function than inextensive procedures.

*The Blood Pressure.* — Reference will be made later to the frequency of lasting blood pressure reduction after sympathectomies and to clinical judgments which have been made regarding the incidence of success and failure.

The immediate effect of sympathectomy in hypertensive patients is to induce an acute fall of blood pressure, which occurs as the nerves are cut and which may reduce the blood pressure temporarily to hypotensive levels. Pressor agents are sometimes required to maintain vascular tone, but [illegible]
measures after 12 [illegible]
the blood pressur[illegible]
rarely does it maintain the low levels observed in the first few postoperative days. It seems necessary to conclude either that the sympathetic connections which remain intact have assumed a compensatory rôle, or that some other physiological mechanism has led to recovery of vascular tone (see Chapter VIII).

A part of the blood pressure fall after a sympathectomy operation is due to a non-specific effect. Almost any substantial surgical procedure, apart from blood loss or nerve section, may lower the blood pressure of a hypertensive patient for periods of up to a month, or occasionally for longer. We have seen this repeatedly. Furthermore, in patients on treatment with ganglion blocking drugs there is a decrease in the amount of drug required which may last for [illegible]
Following sym[illegible]
prominent, [illegible]
of time ort[illegible]
degree indefinitely. [illegible] but it may persist to some

The extent [illegible]
for one [illegible]
Evelyn e[illegible] showed, the blood pressure levels of surviving patients tend to be less satisfactory at five than at two years after

from D4 to L3 by a trans-thoracic approach. It is usually carried out in three or four stages.

## Complications of Surgery

The mortality of sympathectomy varies from under 2 per cent in mild cases to 10 per cent or more in severe cases. The thoracic operation may be followed by pleural effusions, haemothorax and occasionally empyema. An important complication is the occurrence of post-

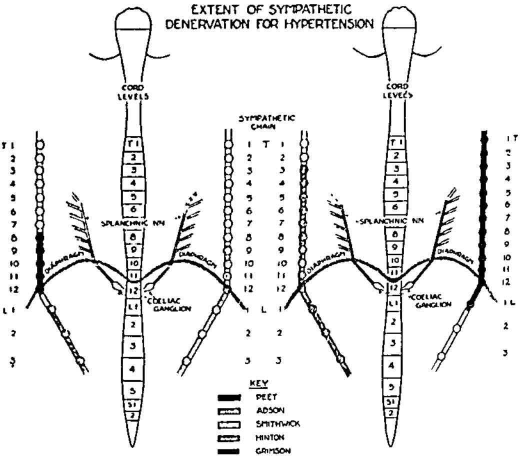



Fig XIV 1

hypertension The approaches of Peet and nton and Grimson are transpleural Quite l approach, with the extent of denervation used by Hinton (de Takats, G, Julian, O. C, and Fowler, E F, Surgery, 24 469, 1948).

operative pains in relation to the wound These are frequent and severe and may require morphine.

In high thoracic denervations, Horner's syndrome and nasal congestion are likely to be present after the operation. Platt and Stanbury (1950) describe the occurrence of post-operative cardiac failure and Morrissey et al. (1953) mentioned the occurrence of post-

operative breathlessness. Hillestad (1955) referred to the development of angina on lowering of the blood pressure in some patients. Kahn (1954) mentions chylothorax as a possible complication of sympathectomy.

## CLINICAL RESULTS OF SYMPATHECTOMY

### Physiological Effects

Although the extents of sympathectomy operations differ, the resulting circulatory and other clinical manifestations are of the same kind. Patients show individual differences in the degree to which they are affected by sympathectomy; and also extensive sympathectomies are more likely to induce substantial changes in autonomic function than inextensive procedures.

*The Blood Pressure.* — Reference will be made later to the frequency of lasting blood pressure reduction after sympathectomies and to clinical judgments which have been made regarding the incidence of success and failure.

The immediate effect of sympathectomy in hypertensive patients is to induce an acute fall of blood pressure, which occurs as the nerves are cut and which may reduce the blood pressure temporarily to hypotensive levels. Pressor agents are sometimes required to maintain vascular tone, but usually there is no further need for such restorative measures after 12 hours. In the month or so following sympathectomy the blood pressure is usually well below the pre-operative level, but rarely does it maintain the low levels observed in the first few post-operative days It seems necessary to conclude either that the sympathetic connections which remain intact have assumed a compensatory rôle, or that some other physiological mechanism has led to recovery of vascular tone (see Chapter VIII).

A part of the blood pressure fall after a sympathectomy operation is due to a non-specific effect. Almost any substantial surgical procedure, apart from blood loss or nerve section, may lower the blood pressure of a hypertensive patient for periods of up to a month, or occasionally for longer. We have seen this repeatedly. Furthermore, in patients on treatment with ganglion blocking drugs there is a decrease in the amount of drug required which may last for [illegible]
Following [illegible]
prominent [illegible]
of time or [illegible]
degree indefinitely. [illegible] but it may persist to some

The extent to which a degree of blood pressure reduction is preserved for one or two years after sympathectomy varies greatly but, as Evelyn et al. (1949) showed, the blood pressure levels of surviving patients tend to be less satisfactory at five than at two years after

the operation. It is well known that in many cases the effects of sympathectomy eventually diminish. Mendlowitz and Touroff (1952) found that in the course of time, after sympathectomy, there was an increase in the non-neurogenic tone, and also some return of sympathetic nerve function.

*Cerebral circulation.* — Following sympathectomy the innervation of cerebral vessels remains intact, while the sympathetic supply to some lower parts of the body is interfered with. Under these circumstances the cerebral circulation should receive a smaller proportion of the cardiac output.

Shenkin et al. (1948) found, however, that after a thoracolumbar sympathectomy, the cerebral oxygen intake and blood flow of hypertensive patients in the supine posture did not differ from the preoperative level; there was, therefore, a fall in the cerebral vascular resistance. Hafkenschiel et al. (1951) compared untreated patients with essential hypertension with patients who had been treated by sympathectomy. Normally a 20 degree head-up tilt is associated with relaxation of the cerebral blood vessels. In essential hypertension there was incomplete relaxation of the cerebral blood vessels with head-up tilt, but no striking difference in the results was observed between untreated cases and those who had had a sympathectomy.

*Retinal Circulation.* — There have been a number of reports of relaxation of constricted retinal arterioles following sympathectomy (Page and Heuer, 1937; Hillestad, 1955; Allen and Adson, 1938) but Harland and D'Abreu (1949) did not always observe release of the retinal artery spasm

*Renal Circulation.* — Although improvement in the renal blood flow was at one time thought to explain some of the beneficial effects of sympathectomy, subsequent work [7, 17, 30, 66] indicates that no striking change takes place in the renal circulation. Allen and Adson (1938) found no impairment of the renal function following sympathectomy.

*Splanchnic Circulation.* — Wilkins et al (1949) found that after sympathectomy the hepatic portal blood flow (bromsulfalein method) was first increased and later returned towards the original level. They observed that the normal vasoconstriction in response to assumption of the erect posture was diminished

*Limb Circulation.* — It seems to be generally agreed that after sympathectomy for hypertension the feet tend to be warmer [5], but the hands are often colder [64]. Not infrequently a mild Raynaud phenomenon of the hands may make its appearance after sympathectomy [5, 7, 64, 82]. In the course of time the sympathetic supply to a limb following regional sympathectomy regenerates to some extent (Barcroft and Swan, 1953).

*Effect on Pressor Reflexes.* — The occurrence of considerable orthostatic hypotension in the month or so following sympathectomy has

been referred to already. It is indicative of lack of the normal increase in sympathetic tone which should occur on assumption of the erect posture. The occurrence of postural hypotension may be associated also with an inability of the venous tone to increase on assumption of the upright posture.

Wilkins et al. (1948, 1949) described reduction in other sympathetic reflexes, namely, in the normal overshoot of the blood pressure following the Valsalva manoeuvre, and following rapid restoration of the horizontal posture in a patient who has been resting, head up, on an inclined plane (the so-called tilt-back overshoot).

Reports on the effects of sympathectomy upon the response to the cold pressor test of Hines vary. Allen and Adson (1937) and Smithwick (1948) found the response to the cold pressor test was diminishing especially, according to Smithwick, when the test was made with the patient in the standing posture. Bechgaard and Hammarström (1950), however, found no important difference between the responses before and after operation.

*Effects on the Heart.* — No great change in the resting cardiac output follows the usual forms of sympathectomy [1, 89, 103]. In the majority of sympathectomy operations, which do not involve the upper dorsal ganglia, a postural tachycardia is present after the operation which represents the activity of parts of the regulatory mechanism which have not been impaired by surgery, and which are regulating against the orthostatic fall of blood pressure. If, however, the Grimson operation, or some other operative procedure involving [illegible]

[illegible] of the heart.

Probably the breathlessness and tachycardia on exertion or even on standing upright noted by Morrissey et al. (1953) is due, at least in part, to the effect of such regulatory mechanisms as remain upon the heart. Fishberg (1954) also noted the orthostatic tachycardia and De Takats, Julian and Fowler (1948) confirmed the observation that orthostatic tachycardia is eliminated by high thoracic ganglionectomies.

*Other effects of Sympathectomy.* — Loss of sweating over the denervated regions is to be expected and has been used [illegible]

Several manifestations which occur after sympathectomy appear to be due to the overaction of the unopposed parasympathetic nerve supply. Unopposed parasympathetic activity was probably [illegible] for the occurrence of [illegible]

Morrissey et al. (1953 [illegible]

pathectomy had exter [illegible]

Alimentary symptoms may follow the unopposed parasympathetic activity. Not infrequently the number of bowel motions is increased, though diarrhoea is not a usual effect [5, 7, 44]. Hillestad (1955) records that a number of patients previously troubled by constipation had relief from this complaint after sympathectomy.

Recurrences of peptic ulcer have been reported by Blegen and Kintner (1949), and by Mason and Pollard (1949). Sympathectomy may suppress ulcer pain [61], and Ray (1949) and Weeks et al. (1946) have reported the perforation of painless duodenal ulcers following bilateral thoracolumbar sympathectomy and vagotomy.

*Alterations in Sexual Function.* — The more prominent manifestations are found in the male. Operative procedures which do not go below $L_1$ are likely to cause no disturbance in sexual function. Rose (1953) found that only a proportion of bilaterally sympathectomized patients had disturbance of function. Apparently the risk begins with bilateral ganglionectomy at $L_2$. Rose (1953) found that not all patients who had a bilateral removal of $L_{1,\ 2}$ and $_3$ were sterile. Erection is usually preserved. There may be a loss of ejaculation only (Hillestad, 1955) and this may be associated with a reflux of semen into the bladder.

Bechaard and Hammarström (1950) have described loss of orgasm in women.

## Clinical Apprisals

In general, as might be expected, it has been thought that the more extensive sympathectomies are associated with the greater expectation of a fall in blood pressure. A variety of surgical procedures have been used; and personal skill, and even more the selection of cases, influence the results obtained. As Schaaf in his 1954 review points out, opinions and emotions about sympathectomy for hypertension still range from enthusiastic to dejected with the weight of opinion tending to restrict the field of surgery. Smithwick and Thompson (1953) reported their results in 1,266 hypertensive patients treated by thoracolumbar splanchnicetomy with important reductions in the mortality in all Smithwick severity grades, and with comparatively few contraindications to surgery. At the other end of the scale is a careful study by Platt and Stanbury (1950) who say, "We believe that the majority of cases of essential hypertension can, from the point of view of sympathectomy, be divided into two classes — namely, those which are too mild to warrant the use of this serious operation, those which are too severe, too old, or too arteriosclerotic to benefit from it." They consider that there is a small middle group in which sympathectomy, even judging by the strictest of standards, produced real and apparently lasting benefits. The experience in our clinic has not been extensive but

has inclined us to take up a position closer to that of Platt and Stanbury than to that of Smithwick.

It is of interest to refer to two evaluations of the results of sympathectomy, both from the Massachusetts General Hospital, by Evelyn, Alexander and Cooper (1949) and White, Dimond and Williams (1950). Evelyn et al. studied patients in the public wards of the hospital, a large number of them having been operated on by Smithwick. Evelyn and his co-workers found that in 100 patients who had been followed for five years after the operation, the blood pressures were reduced to normal in 8 per cent and showed significant reductions in an additional 13 per cent. The results in 79 per cent were unfavourable in that the blood pressures were not significantly lower than the pre-operative pressures in 52 per cent, and 27 per cent of the patients were dead. Comparing five year with two year follow-ups on the same patients it seemed that the results became less favourable as a longer period of time elapsed after the operation. Evelyn's analysis was made on the basis of clinic blood pressures, whereas Smithwick relied on blood [illegible]

[illegible] made an important point, namely, that in many patients who had had a sympathectomy the blood pressure rose high on visits to the doctor's office or clinic, but much lower blood pressures were obtained when home readings were taken. Home readings sometimes revealed a useful effect from sympathectomy which was not apparent when the casual blood pressures were measured in an outpatient clinic. This enhanced lability of the blood pressure is also a feature of treatment by ganglion blocking drugs and large falls of blood pressure may be concealed unless either home blood pressures are taken or the clinic blood pressures are taken throughout the day by a technician service. It is my impression that the degree of improvement in the blood pressure after sympathectomy has sometimes been underestimated, partly because of the blood pressure raising effect of the clinic environment and also because, until recently, the therapeutic importance of the postural falls of blood pressure and of the lessened rise with exercise have been underestimated.

In the follow-up by White, Dimond and Williams (1950), 50 patients operated on in private by Dr. R. H Smithwick were compared with 50 control hypertensive patients not subjected to sympathectomy. The two groups of cases were composed of patients with important cardiovascular complications but patients with renal insufficiency were excluded Of the 50 surgical patients 12 died, and of the 50 patients treated medically 41 died.

Smithwick and Thompson (1953) have reviewed their results together with a control series of patients who were not operated upon. The two series were not exactly comparable, however, as 61 per cent of

the control series were men and there were only 47 per cent of males in the surgical series. The average age of the medical series was 45 and of the surgical series 42. Smithwick concludes that 45 per cent of his living operated patients have a significantly lowered basal blood pressure in the early years after operation; 55 per cent have no change or show an increase of blood pressure; he thinks the outlook of his patients has been improved by operation.

Hillestad (1955) used the Smithwick operation in 52 patients. He obtained a fall of blood pressure in 70 per cent of patients and improvements in clinical manifestations.

Zintel et al. (1955a, b) use the Smithwick classification and obtain a 5-year survival in 63 per cent of group 4 and in 45 per cent of group 5 (see earlier papers of Smithwick).

Bechgaard and Hammarström (1950) made a careful comparison between a surgical series and a collection of matched medical cases. They divide their cases into seventy groups and find that the prognosis is significantly improved in the severe groups and that more time must elapse before a decision can be reached in the milder groups. The average drop in the supine pressure about 45 days after operation was 33/19 mm. Hg, and at about 33 months after operation was 26/14 mm. Hg. They found that postural hypotension diminished rapidly after the first year but, as we have observed also, it may persist for several years.

Morrissey (1954) used the Smithwick operation and a modified Grimson operation. He classified his patients by the method of Hammarström and Bechgaard (1950), and his survival times for patients treated surgically were comparable with theirs. Both of these surgical groups regard poor renal function as a contraindication to surgery. Morrissey et al. (1953) do not accept congestive heart failure cases, but Bechgaard advises operation on heart failure cases if good functional capacity has been restored first with digitalis

Grimson et al. (1953) report good survival rates from Grimson's "total" sympathectomy operation, namely, 84.5 per cent at five years and 56.2 per cent at ten to thirteen years. The contraindications to surgical treatment mentioned by this group are: uraemia, encephalopathy with marked increase of intracranial pressure, serious myocardial infarction or cardiac failure, and age over 50. The distribution of their cases in the Keith-Wagener-Barker classification were 20 patients in grade 4, 48 patients in grade 3 and 104 in grade 2. Grimson et al. (1953) consider that the Keith-Wagener-Barker (1939) series of patients are unsuitable for comparison with surgical series as only an occasional one of the Keith-Wagener-Barker group 4 patients under age 50 could have been accepted for sympathectomy.

Hoobler et al. (1950) described the results on 338 hypertensive patients treated with splanchnicectomy. Ninety-eight had blood pres-

sure reductions of more than 20 mm. Hg in their casual diastolic pressure and in 60 patients the authors were confident that the reductions exceeded the range of spontaneous variations. They compared these successful cases with the unsuccessful cases but found no way of predicting from the pre-operative data which of the patients were likely to benefit from surgery.

Five hundred cases operated on by Dr. J. William Hinton were evaluated by Thorpe et al. (1950). The operation used was removal of the sympathetic chain from L3 or 2 to D8 and in some cases a more radical procedure was undertaken. They grouped their cases by Palmer's classification

The classification of Palmer et al. (1948) is a modification of the Keith- [illegible]

[illegible] slight albuminuria or slight changes on microscopical examination of the urine

Grade 2 (Palmer) cases usually have organic changes in the fundi involving the arterioles, the heart may be normal but more usually shows a prominence in the region of the left ventricle and may be definitely enlarged, but is without functional impairment. The kidneys are normal apart from slight degrees of albuminuria or a few formed elements in the sediment. If there is any renal functional impairment at all it is slight.

Grade 3 (Palmer) cases seldom [illegible]
changes and often exudates [illegible]
or markedly enlarged and w[illegible]
failure or of anginal failur[illegible] often shows albuminuria, and renal function is often impaired, though actual rise in the non-protein nitrogen is not common Cerebral accidents may be present in this group

Grade 4 (Palmer) cases include papilloedema as an obligatory sign with or without exudates and haemorrhages Cardiac and renal changes may be present.

They noted excellent results in 9 8 per cent, good in 17.2 per cent, fair in 29 2 per cent, poor in 11 8 per cent, unknown in 9.8 per cent, and 22 2 per cent were dead at the time of follow-up. In groups 1, 2 and 3 they found no statistically significant [illegible]

[illegible] in the operated group.

The mortality experience compared with the series of medically treated cases by Palmer was:

| | Survival rates | |
|---|---|---|
| | Surgical cases | Medical controls |
| Group 1 . . . . | 91.7 | 97 |
| Group 2 . . . . | 88.8 | 90 |
| Group 3 . . . . | 74.7 | 75 |
| Group 4 . . . . | 44.6 | 16 |

Palmer (1947), using the classification of cases referred to above, made a careful comparison of the results in a group of medically treated patients with results obtained by surgery. He stated that the number of patients maintaining a favourable result decreases with the elapse of time; so that whereas there were almost 70 per cent of good results early in their experience, these declined to 25 per cent when the patients were followed for three to five years or more. Even so, improvement was twice as frequent in the surgical series as in the medical series, the latter being treated by such means as were available in 1948. He concluded that at the time of writing sympathectomy was the treatment of choice for malignant hypertension. He had the impression that an important part of the benefit came from the orthostatic falls in the blood pressure level.

Platt and Stanbury (1950) state that a significant reduction of blood pressure was achieved in only 11 out of 80 surgical cases in which the Boyd operation predominated, even though the follow-up period was relatively short.

An important point is the statement by Platt and Stanbury (1950) that if the blood pressure by itself is the physician's concern he has little chance of changing it significantly by operation in patients over the age of 45 of either sex, whether the hypertension be moderate, severe, or "malignant". Of Platt and Stanbury's 24 cases with malignant hypertension (14 males, 10 females) papilloedema disappeared in 12, sometimes without appreciable change in the blood pressure. Of these patients 57 per cent of the males and 30 per cent of the females died at or following the operation. Platt and Stanbury noted that dyspnoea on exertion occurred post-operatively in patients who had perfect exercise tolerance before operation. There were a number of post-operative sequelae but the patients who had had incapacitating headaches beforehand were emphatic in their assertion that the operation was worthwhile.

Peet and Isberg (1948) observed their results in 143 patients with malignant hypertension who were followed for five to twelve years after surgical treatment. 17.5 per cent of the patients were between 50 and 57 years of age, the remainder 49 or under. Their operative mortality was 10 per cent. Of the patients surviving the operation 54 per cent survived one year, 40 per cent two years, 30 per cent three years, 26 per cent four years and 21.6 per cent five years. A retinal examination of 10 living patients was made and the papilloedema had disappeared in all of these.

Pickering, Wright and Heptinstall (1952) describe three interesting cases of malignant hypertension verified by renal biopsy and with albuminuric retinitis, in which five or six years after sympathectomy the patients were alive and well with a less severe hypertension, a normal blood urea level, and a normal urea concentration.

Persike et al. (1949) do not accept the usual view that substantial renal disease is a contraindication to the use of sympathectomy. They have used bilateral splanchnicetomy and lumbodorsal sympathectomy and obtained relief of manifestations in certain renal cases. The outlook of advanced renal cases is in any case bad. Our experience, and that of many others, has been that the reduction of blood pressure by medical means in severe renal cases affords a degree of symptomatic relief, even though the ultimate outlook is probably unchanged.

Newell and Smithwick (1947) and Peet and Isberg (1949) expressed the opinion that pregnancy may be tolerated after splanchnicectomy for essential or malignant hypertension.

[illegible] control patients treated medically, but prior to the use of active hypotensive drugs. The mortality after 10 to 15 years was 25/50 for the sympathectomy group and 48/50 for the medically treated group.

Fishberg (1948) gave an analysis of the value of sympathectomy in 119 selected patients. In 1948 he considered that sympathectomy was indicated in less than 4 per cent of patients with essential hypertension In well selected patients, retinopathy cleared in 12 out of 17 patients. The diastolic pressure was reduced by 25 per cent or more in 30 patients [illegible]
ad[illegible]
sm[illegible]
tie[illegible] respond to medical treatment. He does not think sympathectomy should be advised in asymptomatic patients, however high the blood pressure may be, and it should rarely be advised after the age of 50.

### Relief of Clinical Manifestations

The evidence that clinical improvements occur in a proportion of cases after sympathectomy is strong. There is general agreement that headache is nearly always relieved [18, 64, 67, 72, 75, 79, 82, 97].

Anginal pains may be improved or made worse or develop for the first time after sympathectomy. Hillestad (1955) had 54 patients treated by sympathectomy. Twelve patients had [illegible]
operation [illegible]
2 w[illegible]
sho[illegible]
by several other authors. [illegible] variable results are described

Electrocardiographic improvement has been described by several authors. Allen and Adson (1938); Peet, Wood[illegible]
White et al. [illegible]
ar[illegible]

the T wave which sometimes became positive following sympathectomy. Decreases in the heart size have been described by Allen and Adson (1938), Bechgaard and Hammarström (1950), Boyer and Hewitt (1950) and Peet and Isberg (1948), and Peet, Woods and Braden (1940).

Many surgeons have not accepted heart failure cases in their series but there is evidence that improvement may take place after the blood pressure has been reduced by sympathectomy; thus Chavéz and Méndez (1949) described the effects of sympathectomy in 11 patients, 8 of whom improved considerably. Isberg and Peet (1948), while less definite in their recommendation, had 16 patients with heart failure treated by sympathectomy and five of them survived for five years. Zintel et al. (1955a) also obtained benefit in heart failure cases.

This confirms the recommendation of White (1945) who stated categorically that hypertensive heart disease was an indication of the need for operation. Our own results with drug therapy indicate the very great improvements in the condition of heart failure patients which can be obtained even in the absence of digitalis, mercurial diuretics and a salt-free diet, merely by effective reduction of blood pressure levels.

Of all the objective changes, those in the retina appear to be the most significant. Decreases or disappearance in papilloedema have been described by almost all authors who report a considerable series of cases [7, 36, 42, 44, 59, 64, 67, 72, 74, 75, 79, 82]. Additionally, decrease in other potentially reversible features such as retinal exudates and haemorrhages are likewise reported frequently [5, 7, 36, 42, 44, 59, 64, 67, 82, 97]. While there is not the slightest doubt that improvements in the state of the retina are not unusual, it should be borne in mind that sympathectomy may affect the retina by allowing sympathetic tone to be maintained in the region of the head at a time when the blood pressure is somewhat reduced. Such an explanation of the improvement gains no support from the observation which has been made by several observers that spasm of the retinal arteries may be lessened following sympathectomy. This observation is difficult to explain.

According to Ray (1949) it seems possible that sympathectomy may have decreased the incidence of cerebral vascular accidents.

### Comments of the Effects of Sympathectomy in Hypertension

Some patients have been benefited by surgery in that they have had [illegible] manifestations, such [illegible] ive heart failure. In a variable proportion of patients there have been falls of blood pressure beyond those likely to be the result of spontaneous variation. Estimates of the number of patients who have benefited vary greatly. Some at least of the more optimistic reports appear to have

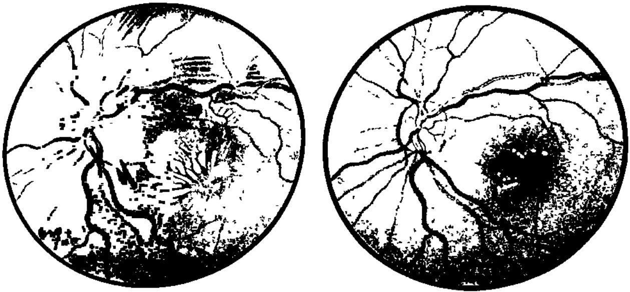


Fig. A.

Drawings of the fundus of a woman aged 58 with chronic pyelonephritis before and eight months after nephrectomy. The left hand drawing shows papilloedema, numerous haemorrhages, hard exudates and some soft exudates. The right hand drawing shows a few speckles of hard exudate remaining.

Reproduced from Rosenheim, M. L., Brit. med. J., 2, 1181, 1954.

the T wave which sometimes became positive following sympathectomy. Decreases in the heart size have been described by Allen and Adson (1938), Bechgaard and Hammarström (1950), Boyer and Hewitt (1950) and Peet and Isberg (1948), and Peet, Woods and Braden (1940).

Many surgeons have not accepted heart failure cases in their series but there is evidence that improvement may take place after the blood pressure has been reduced by sympathectomy; thus Chavéz and Méndez (1949) described the effects of sympathectomy in 11 patients, 8 of whom improved considerably. Isberg and Peet (1948), while less definite in their recommendation, had 16 patients with heart failure treated by sympathectomy and five of them survived for five years. Zintel et al. (1955a) also obtained benefit in heart failure cases. This confirms the recommendation of White (1945) who stated categorically that hypertensive heart disease was an indication of the need for operation. Our own results with drug therapy indicate the very great improvements in the condition of heart failure patients which can be obtained even in the absence of digitalis, mercurial diuretics and a salt-free diet, merely by effective reduction of blood pressure levels.

Of all the objective changes, those in the retina appear to be the most significant. Decreases or disappearance in papilloedema have been described by almost all authors who report a considerable series of cases [7, 36, 42, 44, 59, 61, 67, 72, 74, 75, 79, 82]. Additionally, decrease in other potentially reversible features such as retinal exudates and haemorrhages are likewise reported frequently [5, 7, 36, 42, 44, 59, 64, 67, 82, 97]. While there is not the slightest doubt that improvements in the state of the retina are not unusual, it should be borne in mind that sympathectomy may affect the retina by allowing sympathetic tone to be maintained in the region of the head at a time when the blood pressure is somewhat reduced. Such an explanation of the improvement gains no support from the observation which has been made by several observers that spasm of the retinal arteries may be lessened following sympathectomy. This observation is difficult to explain.

According to Ray (1949) it seems possible that sympathectomy may have decreased the incidence of cerebral vascular accidents.

## Comments of the Effects of Sympathectomy in Hypertension

Some patients have been benefited by surgery in that they have had [illegible] ...ons, such [illegible] ...ive heart [illegible] ...n falls of [illegible]

greatly. Some at least of the more optimistic reports appe[illegible]

been influenced by the inclusion of mild cases, by comparison with collections of medical cases of greater severity, with different age groups, or with higher proportions of males (e.g. the Keith-Wagener group has 65 per cent males). The strongest evidence of benefit is in patients with malignant hypertension where life is prolonged and papilloedema and other exudative retinal changes are dispersed in a proportion of cases which is much higher than the proportion in which improvement occurs spontaneously. It may at first seem to be remarkable that life is prolonged and retinal and other improvements occur in people whose blood pressures do not seem to have diminished appreciably. These apparent anomalies may be explained to some extent as follows:

1. Blood pressure reductions are often concealed by emotional rises of blood pressure, so that clinic blood pressures may be high even when home blood pressures are reduced.

2. When blood pressures after sympathectomy are only measured in the supine posture the observer will overlook reductions which are present if the patient is sitting or ambulant. Orthostatic falls of pressure are useful therapeutically and patients may have lower post-exercise pressures

3. Reversal of a malignant phase may occur post-operatively when the blood pressure is much reduced. In patients whose blood pressures rise again the clinical manifestations of malignant hypertension may not recur

4. Relief of [illegible]
vascu[illegible]
inner[illegible] [illegible] vessels with section of the sympathetic supply to lower parts of the body. This should cause a decrease in the cerebral blood flow — at least with patients in the erect posture.

Although definite benefit follows sympathectomy in at least some cases, it is the view of our clinic that there are few or no indi[illegible]

[illegible] were ineffective in reducing sufficiently the side effects of ganglionic blockade. Recently the [illegible]
and oth[illegible]
has gre[illegible]
that ev[illegible] uncomfortable under the best régime which can be devised for them. In such patients I have at times contemplated sympathectomy; not with much hope that by itself it would induce a comparable reduction in blood pre[illegible]
experience [illegible]
the eff[illegible]

[illegible] drugs,

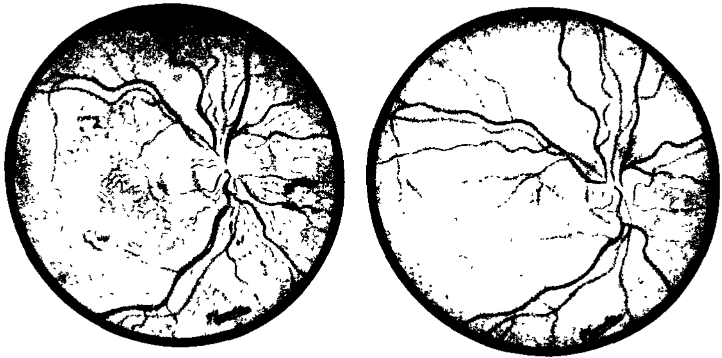


Fig B

Drawings of the *fundus* of a man aged 28 with chronic nephritis before and one year after bilateral thoraco-lumbar sympathectomy

The left hand drawing shows haemorrhages, soft exudate and hard exudate. The right hand drawing illustrates the disappearance of these

Reproduced from Rosenheim, M L., Brit med J., 2 1181, 1954.

been influenced by the inclusion of mild cases, by comparison with collections of medical cases of greater severity, with different age groups, or with higher proportions of males (e.g. the Keith-Wagener group has 65 per cent males). The strongest evidence of benefit is in patients with malignant hypertension where life is prolonged and papilloedema and other exudative retinal changes are dispersed in a proportion of cases which is much higher than the proportion in which improvement occurs spontaneously. It may at first seem to be remarkable that life is prolonged and retinal and other improvements occur in people whose blood pressures do not seem to have diminished appreciably. These apparent anomalies may be explained to some extent as follows:

1. Blood pressure reductions are often concealed by emotional rises of blood pressure, so that clinic blood pressures may be high even when home blood pressures are reduced.

2. When blood pressures after sympathectomy are only measured in the supine posture the observer will overlook reductions which are present if the patient is sitting or ambulant. Orthostatic falls of pressure are useful therapeutically and patients may have lower post-exercise pressures.

3. Reversal of a malignant phase may occur post-operatively when the blood pressure is much reduced In patients whose blood pressures rise again the clinical manifestations of malignant hypertension may not recur.

4 Relief of headache, and perhaps a decreased incidence of cerebral vascular accidents, might be due to the preservation of the sympathetic innervation of cerebral vessels with section of the sympathetic supply to lower parts of the body. This should cause a decrease in the cerebral blood flow — at least with patients in the erect posture

[illegible]

cas[illegible]

syn[illegible] hypertension, provided facilities are available for the adequate treatment of hypertensive patients by drugs. Indeed, in a period of five years the only indications I have seen for sympathectomy among the patients referred to me have been in exceptional cases where pharmacological means were ineffective in reducing sufficiently the side effects of ganglionic blockade. Recently the use of reserpine and other Rauwolfia alkaloids in conjunction with ganglionic blockade has greatly reduced the incidence of parasympathetic side effects, so that even fewer patients remain who are uncomfortable under the best régime which can be devised for them. In such patients I have at times contemplated sympathectomy; not with much hope that by itself it would induce a comparable reduction in blood [illegible]

experience [illegible]

the effects [illegible]

[illegible] other drugs,

are appreciably enhanced in people who have previously had a sympathectomy. The idea, therefore, was to advise sympathectomy in hope of reducing the side effects of drug therapy. In the two or three patients where I have had occasion to suggest sympathectomy for this purpose, I have been informed by the patients that the side effects were not bad enough for them to contemplate a surgical procedure. Thus in six years, and in approximately 450 patients who have come to us for treatment, surgery had been contemplated by us in two or three patients but rejected by the patients.

In some patients who cannot be induced to take sufficient care with drug therapy there may be a case for sympathectomy; but the need for drug therapy will not usually be avoided. The main advantage is that after sympathectomy drug therapy is usually easier to manage.

## ADRENALECTOMY ALONE AND IN COMBINATION WITH SYMPATHECTOMY

For many years sub-total adrenalectomy was used in an attempt to relieve hypertension or to improve upon the results of sympathectomy [3, 21, 25, 57, 65], but the results were not definite.

In 1050 Green et al. described the results of a bilateral adrenalectomy performed on a 28-year old woman suffering from both malignant hypertension and diabetes mellitus. The patient survived fifteen months after the operation, the blood pressure having fallen post-operatively to near normal levels. The retinal appearances improved and heart failure, which had been present pre-operatively, only recurred with excessive administration of desoxycorticosterone acetate. The diabetes was also improved, but the control of adrenal insufficiency gave rise at times to anxiety. This pioneer investigation had support from the work of Goldblatt, who had shown that experimental hypertension induced by renal ischaemia required the presence of adrenal cortical hormones for its maintenance.

Further pioneer investigations were made by a group in Philadelphia [49, 50, 51, 105, 107, 110], who studied the effects in severe hypertension of various combinations of sympathectomy and adrenalectomy. Even bilateral sympathectomy and bilateral total or sub-total sympathectomy did not always cause a durable fall in blood pressure, but lasting falls in blood pressure were much more frequent than with sympathectomy alone. It is clear from their results that falls of blood pressure of considerable magnitude occur, that there is a good chance of maintaining the fall, and that certain hypertensive manifestations are often reversed, namely, papilloedema and other exudative retinal changes, and congestive heart failure. Improvements occurred in the electrocardiogram and in the heart size, but in patients with diminished adrenal function, the interpretation of such changes may be difficult.

Great interest attaches to this admittedly experimental procedure for it provides an additional demonstration that effective reduction of the blood pressure is associated with the reversal of many hypertensive manifestations; such reversal appears to take place irrespective of the means employed.

The main objection to adrenalectomy as a practicable means of therapy is that, combined with bilateral sympathectomy or alone it is [illegible]

hazards which an important proportion of patients must expect to encounter. The team of physicians and surgeons at Philadelphia feel confident that they can to handle these difficulties but, as they and Bowers et al. (1953) point out, the patient is dependent on being able to make contact with physicians who have a special knowledge of the subject whenever an illness occurs which involves readjustment of substitution therapy. The cortisone requirement was usually under 25 mg. daily.

Thorn et al (1952) described their experience with 15 patients treated with adrenalectomy. After about eighteen months 9 had died and, [illegible] found [illegible] accon[illegible] from [illegible] who also treated a group of severe hypertensive patients by either adrenalectomy or by a combined procedure of sympathectomy and total adrenalectomy. Death occurred in 3 out of 11 patients

## Comment on the use of Adrenalectomy Alone or in Conjunction with Sympathectomy

The results of bilateral sub-total or total adrenalectomy in the treatment of hypertension are of great interest for, although hypertension may persist after such operations, it usually happens that blood pressure reductions are obtained. The character of the improvement recorded by the Philadelphia group makes it clear that considerable falls of blood pressure which they report have been associated with reversal of a number of well-known hypertensive manifestations.

Adrenalectomy is associated with loss of sodium and decrease of blood volume. It is doubtful whether these changes explain the considerable falls of blood pressure which occur. Cerebral vascular resistance is reduced by the adrenalectomy (Hafkenschiel et al., 1954).

Jeffers et al. (1954) mention the following indications for operation involving sympathectomy and adrenalectomy. These are:

(1) an average diastolic pressure of 120 mm. Hg or more;

(2) a failure to respond to intensive medical therapy;
(3) evidence of progressive damage to the heart, kidneys, brain or eyes.

All three of these indications should be present before operation is resorted to. Among the contraindications are important impairments of renal function.

I have had no personal experience with adrenalectomy, but failure to respond to intensive medical therapy when adequately conducted is extremely rare in my experience, and, when present, is usually associated with terminal renal failure. My [illegible] is not to be advised as a treatment f[illegible] tension.

## Lobotomy and Leukotomy

In some, but not in all, hypertensive patients the operation of leukotomy or of lobotomy has been associated with a decrease in the blood pressure, but such falls in blood pressure are by no means always of long duration (Greenblatt et al., 1947). There is no reason to advocate procedures involving a change in personality except in patients who would otherwise qualify for them. Tibbetts (1949) records a patient whose blood pressure fluctuated between 170/100 and 260/160 and had adequate indications for leukotomy apart from the hypertension. Her blood pressure following the operation lay between 160/90 and 140/80. She was followed for a period of sixteen months and her blood pressure was still 160/100 to 140/95. Another patient who exhibited a long lasting fall of blood pressure was described by Freeman and Watts (1950). The pressure fell from 240/120 to 160/100, stayed about this level for eight years and then rose to 250/130.

## Various other Surgical Procedures

The treatment of aortic coarctation by surgery is associated with a fall of the arm blood pressure but not always to fully normal levels.

It is of interest that an arteriovenous fistula was used by Martorell (1951) to lower the blood pressure. He does not recommend the procedure.

## References

1 Adams, W., Alving, A. S., Sandiford, I., Grimson, K. S., and Scott, C. L. The effect of bilateral paravertebral sympathectomy on the cardiorenal system in essential hypertension Amer J Physiol, 133 190, 1941.

2 Adson, A. W., and Brown, G. E. Malignant hypertension Report of case treated by bilateral section of anterior spinal nerve roots from sixth thoracic to second lumbar, inclusive J Amer. med Ass, 102: 1115, 1934.

3 Adson, A. W., Craig, W. McK., and Brown, G. E. Surgery in its relation to hypertension Surg. Gynec. Obstet., 62: 314, 1936

4 ALLEN, E. V., and ADSON, A. W. Physiologic effects of extensive sympathectomy for essential hypertension Amer. Heart J., 14: 415, 1937.
5 ALLEN, E. V., and ADSON, A. W. Physiologic effects of extensive sympathectomy for essential hypertension· Further observations. Ann. intern. Med., 11: 2151, 1938.
6 BARCROFT, H., and SWAN, H. J. C. Sympathetic control of human blood vessels Edward Arnold & Co., London, 1953
7 BECHGAARD, P., and HAMMARSTRÖM, S. Surgical treatment of arterial [illegible] 155, 1950
8 [illegible] gravation of a gastric ulcer [illegible] J. Amer. med. Ass., 133, [illegible]
9 BOWERS, R. F., KNOX, F. H., Jr., and GENDEL, B. R. Adrenalectomy for hypertension — Advantages of the anterior abdominal approach. Surgery, 34: 664, 1953
10 BOY[illegible]
11 BOY[illegible] vector analysis of the electrocardiogram in hypertension before and immediately after bilateral lumbodorsal sympathectomy Amer Heart J., 40: 1, 1950
12 BRIDGES, W. C., JOHNSON, A. L., SMITHWICK, R. H., and WHITE, P. D. Electrocardiography in hypertension — Study of patients subjected to lumbodorsal splanchnicectomy J. Amer. med. Ass., 131: 1476, 1946
13 BRIDGES, W. C., and WHITE, P. D. The treatment of diastolic hypertension Med. Clin. N. Amer., 31. 1106, 1947
14 CHAPMAN, E. M., KINSEY, D., CHAPMAN, W. P., and [illegible]
15 CHAVEZ, I., and MÉNDEZ, L. Surgical treatment of hypertensive heart disease and of heart failure of hypertension. Amer Heart J., 37: 523, 1949
16 CHRIS, S. M. Sympathectomy for hypertension Brit. med. J., 1: 665, 1951
17 CORCORAN, A. C., and PAGE, I. H. Renal blood flow and sympathectomy in hypertension Arch. Surg. (Chicago), 42: 1072, 1941.
18 CRAIG, W. McK. Evaluation of treatment of hypertension J. Amer. med. Ass., 139 1239, 1949.
19 CRAIG, W. McK., and BROWN, G. E. Experiments on the control of blood pressure by operation on the sympathetic nervous system. Proc. Mayo Clin., 7: 61, 1932
20 CRAIG, W. McK., and BROWN, G. E. Resection of splanchnic nerves in cases of hypertension Proc. Mayo Clin., 8· 373, 1933
21 CRILE, G. Indications for [illegible] glands
22 CRILE, G. Th[illegible] essential
23 D'ABREU, F. [illegible] hypertension. Lancet, 1: 1164, 1953
24 D'ABREU, F. The surgical treatment of hypertension Med. Press, 231: 165, 1954
25 DE COURCY, J. L. Subtotal bilateral adrenalectomy for hyperadrenalism (essential hypertension). Ann. Surg., 100· 310, 1934.
26 DE TAKATS, G., JULIAN, O. C., and FOWLER, E. F. The surgical treatment

of essential hypertension. IV. Case selection and technique as influencing results. Surgery, 24: 469, 1948.

27 EVELYN, K. A., ALEXANDER, F., and COOPER, S. R. Effect of sympathectomy on blood pressure in hypertension: A review of 13 years' experience of the Massachusetts general hospital. J. Amer. med. Ass., 140: 592, 1949.

28 FISHBERG, A. M. Sympathectomy for essential hypertension J. Amer. med. Ass., 137: 670, 1948.

29 FISHBERG, A. M. Hypertension and nephritis. Lea and Febiger, Philadelphia, 1954, 4th edn.

30 FOA, P. P., WOODS, W. W., PEET, M. M., and FOA, N. L. Effective renal blood flow, glomerular filtration rate and tubular excretory mass in arterial hypertension. II. Effect of supra-diaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy. Arch intern Med., 71: 357, 1943.

31 FREEMAN, W., and WATTS, J. W Psychosurgery in the treatment of mental disorders and intractable pain. Blackwell Scientific Publications, Oxford, 1950, 2nd edn

32 GLASER, S. Surgery in hypertension Med Press, 224: 143, 1950

33 GREEN, D. M., NELSON, J. N., DODDS, G. A., and SMALLEY, R E Bilateral adrenolectomy in malignant hypertension and diabetes. J. Amer med Ass., 144: 439, 1950

34 GREENBLATT, M., ARNOT, R. E., POPPEN, J. L., and CHAPMAN, W. P Report on lobotomy studies at the Boston Psychopathic Hospital Amer. J Psychiat., 104: 361, 1947

35 GRIMSON, K. S Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in the treatment of hypertension Ann Surg., 114: 753, 1941

36 GRIMSON, K. S., ORGAIN, E. S., ANDERSON, B., BROOME, R A., and LONGINO, F H Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy Ann Surg., 129: 850, 1949

37 GRIMSON, K. S., ORGAIN, E S., ANDERSON, B., and D'ANGELO, G J Total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy for hypertension Ann Surg., 138 532, 1953

38 HAFKENSCHIEL, J. H., CRUMPTON, C W., SHENKIN, H A., MOYER, J. H., ZINTEL, H A., WENDEL, H., and JEFFERS, W. A. The effects of twenty degree head-up tilt upon the cerebral circulation of patients with arterial hypertension before and after sympathectomy J clin. Invest., 30: 793, 1951.

39 HAFKENSCHIEL, J H., FRIEDLAND, C K., and ZINTEL, H A The blood flow and oxygen consumption of the brain in patients with essential hypertension before and after adrenalectomy J. clin Invest., 33 57, 1954.

40 HAMMARSTRÖM, S., and BECHGAARD, P Prognosis in arterial hypertension — Comparison between 251 patients after sympathectomy and a selected series of 435 non-operated patients. Amer J Med., 8 53, 1950

41 HANTSCHMANN, L. Die Behandlung der Hochdruckkrankheiten II Teil Radiologische und Chirurgische Therapie. Dtsch med Wschr., 78 56, 1953

42 HARLAND, J C., and D'ABREU, F. Lumbo-dorsal sympathectomy in severe hypertension: An interim survey Brit. med. J., 1: 1019, 1949

43 HEUER, G. J., and GLENN, F Evaluation of surgical treatment of hypertension. N Y. St. J. Med., 41: 1922, 1941

44 HILLESTAD, L. Surgical treatment of arterial hypertension. Acta med Scand., 150: 417, 1955.

45 HINTON, J. W., and LORD, J. W., Jr Prognostic value of sodium amytal test in hypertension treated by thoracolumbar sympathectomy. N. Y. St. J. Med., 46: 1015, 1946.

46 HOOBLER, S W., MANNING, J. T, PAINE, W. G, HELCHER, P. O, McCLELLAN, S. G., RENFERT, H., Jr., KAHN, E A., and PEET, M M. Observations on sixty patients with hypertension successfully treated by splanchnicectomy. Univ. Mich. med. Bull, 16: 381, 1950.

47 HOOBLER, S. W., MANNING, J. T., PAINE, W. G., McCLELLAN, S G., HELCHER, P. O, RENFERT, H., Jr., PEET, M M., and KAHN, E. A. The effects of splanchnicectomy on the blood pressure in hypertension: A controlled study. Circulation (N Y.), 4: 173, 1951.

48 ISBERG, E. M., and PEET, M. M. The influence of supradiaphragmatic splanchnicectomy on the heart in hypertension. Amer. Heart J., 35: 567, 1948

49 JEFFERS, W. A., ZINTEL, H. A., HAFKENSCHIEL, J. H., DOHAN, F. C., and KEFFER, N J The blood pressure of patients with hypertension after subtotal adrenalectomy: Relationship to the amount of residual adrenal tissue and substitution therapy. J. clin. Invest., 30: 652, 1951.

50 JEFFERS, W A, ZINTEL, H A, HAFKENSCHIEL, J. H., HILLS, A. G., SELLERS, A M, and WOLFERTH, C C. Evaluation of adrenal resection and sympathectomy in ninety-nine persons with hypertension. J Amer med Ass., 153: 1502, 1953

51 JEFFERS, W A, ZINTEL, H A, HILLS, A G, HAFKENSCHIEL, J. H. LANGFELD, S B, SELLERS, A M, and WOLFERTH, C. C. Further observations on patients with severe hypertension subjected to adrenal resection and sympathectomy Ann intern Med., 41: 221, 1954

52 JOLY, F, MATHIVAT, H, SICOT, J. R., GERBAUX, L., and TOUCHE, M. Les sympathectomies étendues dans l'hypertension artérielle. II. Résultats éloignés Arch Mal Coeur, 48. 245, 1955

53 KAHN, E A Twenty years' experience with the surgery of hypertension New Engl. J Med, 251: 633, 1954.

54 KEITH, N M, WAGENER, H P, and BARKER, N W Some different types of essential hypertension Their course and prognosis. Amer. J. med Sci, 197 332, 1939

55 KOPPERMANN, E, and WALZ, L. Elektrokardiogrammveränderungen bei Hypertonikern vor und nach Sympathikusoperation Verh. dtsch. Ges KreislForsch, 15 136, 1949

56 LANDOWNE, M., ALVING, A S, and ADAMS, W Renal dynamics in "essential" hypertension, the effect of sympathectomy Amer. Heart J, 37, 644, 1949

57 LERICHE, R Du choix d'une méthode dans le traitement chirurgical de l'hypertension artérielle. Arch. méd belges, 95. 575, 1942 Cited by Wolferth, C. C, Jeffers, W A, Lukens, F. D W, Zintel, H. A, and Hafkenschiel, J. H., Ann intern Med, 35 8, 1951.

58 McGAVIN, D Surgery for arterial hypertension Med. Press, 227: 176, 1952

59 MARTIN, R H, and BONAMI, M Les sympathectomies étendues dans l'hypertension artérielle I Résultats immédiats à propos de 122 interventions. Arch. Mal. Coeur, 48 240, 1955

60 MARTORELL, F Arteriovenous fistula as treatment in arterial hypertension. Angiology, 2. 110, 1951.

61 MASON, S C, and POLLARD, H M Peptic ulcer following splanchnicecto-

my: A report of thirteen cases. Surg. Gynec. Obstet., 89: 271, 1949

62 MENDLOWITZ, M., and TOUROFF, A. S. W. The effect of sympathectomy for essential hypertension on the hallucal circulation. Circulation (N.Y.), 5: 577, 1952.

63 MORRISSEY, D. M. Surgical treatment of hypertension. Med. ill. (Lond.), 8: 181, 1954.

64 MORRISSEY, D. M., BROOKES, V. S., and COOKE, W. T. Sympathectomy in the treatment of hypertension: Review of 122 cases Lancet, 1: 403, 1953.

65 NEUHOF, H. Gangliosympathectomy and bilateral hemiadrenalectomy for severest grade of hypertension. Ann Surg, 128: 787, 1948.

66 NEWELL, J. L., and SMITHWICK, R. H. Pregnancy following lumbodorsal splanchnicectomy for essential and malignant hypertension and hypertension associated with chronic pyelonephritis. New Engl. J. Med, 236: 851, 1947.

67 NORTHFIELD, D. W. C. The surgical treatment of hypertension. Proc. roy. Soc. Med., 41: 362, 1948

68 PAGE, I. H., and HEUER, G. J. Treatment of essential and malignant hypertension by section of anterior nerve roots Arch. intern. Med., 59: 245, 1937.

69 PALMER, R. S. Medical evaluation of the surgical treatment of hypertension. J. Amer. med. Ass, 134: 9, 1947.

70 [illegible] ...NG, C R. Prognosis in essen- [illegible] study of 430 patients on [illegible] ...gl J. Med, 239: 990, 1948

71 PEET, M M. The surgical treatment of hypertension. Proc. Calif. Acad. Med, 5: 58, 1935. Cited by Peet, M M, Woods, W. W, and Braden, S., J. Amer. med. Ass, 115. 1875. 1940

72 PEET, M M, and ISBERG, E. M The problem of malignant hypertension and its treatment by splanchnic resection Ann intern Med, 28: 755, 1948

73 PEET, M. M, and ISBERG, E M. Some aspects of hypertensive disease of pregnancy treated by splanchnicectomy. Amer J med. Sci, 217 630, 1949

74 PEET, M. M., WOODS, W. W, and BRADEN, S The surgical treatment of hypertension. Results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy J. Amer. med Ass, 115 1875, 1940

75 PERSIKE, E C, LIPPMAN, R W., ADDIS, T, REICHERT, F L, and RICHARDS V. Surgical treatment for hypertensive complications of advanced renal disease Arch. intern Med, 83 348, 1949

76 PESCHEL, E., and LOHMANN-PESCHEL, R Nitrogen balance on rice diet. J clin. Invest, 29. 455, 1950

77 PICKERING, G W, WRIGHT, A D, and HEPTINSTALL, R H The reversibility of malignant hypertension Lancet, 2 952, 1952.

78 PIERI, G La resezione dei nervi splancnici Ann ital di chir, 6: 678, 1927. Cited by Poppen, J L, and Lemmon, C, J Amer. med Ass, 134: 1, 1947

79 PLATT, R. The surgical treatment of hypertension Proc roy Soc Med., 41: 359, 1948

80 PLATT, R, and STANBURY, S W. Sympathectomy in hypertension Lancet, 1: 651, 1950

81 POPPEN, J. L, and LEMMON, C. The surgical treatment of essential hypertension J Amer. med Ass, 134: 1, 1947

82 RAY, B S The surgical treatment of hypertensive vascular disease. An

analysis of results of thoracolumbar sympathectomy in 300 cases. Med Clin N. Amer, 33: 735, 1949.

83 REVELL, S T. R, BORGES, F. J., YEAGER, G. H, ARNOLD, J. G., and AHLQUIST, R I. Sympatho-adrenal surgery in the malignant phase of essential hypertension Ann intern. Med, 41: 50, 1954.

84 ROSE, S S. An investigation into sterility after lumbar ganglionectomy. Brit. med. J, 1: 247, 1953.

85 ROWNTREE, L. G, and ADSON, A. W. Bilateral lumbar sympathetic neurectomy in the treatment of malignant hypertension: Report of a case J. Amer. med Ass, 85: 959, 1925.

86 SCHAAF, R S Cardiovascular diseases: A review of some significant publications (July 1949 — June 1952). Arch intern. Med., 93: 254, 1954

87 SHENKIN, H. A, HAFKENSCHIEL, J H., and KETY, S S Effects of sympathectomy on the cerebral circulation of hypertensive patients. Arch. Surg (Chicago), 61: 319, 1950.

88 SMITH, E. L, HAYNES, B. W, and EVANS, E. I. The effect of sympa-

89

Surgery, 7: 1, 1940

90 SMITHWICK, R H Surgical treatment of hypertension. Amer. J. Med., 4 744, 1948

91 SMITHWICK, R H. Hypertensive cardiovascular disease: Effect of thoracolumbar splanchnicectomy on mortality and survival rates J. Amer. med Ass, 147: 1611, 1951

92 SMITHWICK, R H, and THOMPSON, J E. Splanchnicectomy for essential hypertension. Results in 1,266 cases. J. Amer. med. Ass, 152. 1501, 1953

93 THOMPSON, J. E. and SMITHWICK, R. H Surgical measures in hypertension. Geriatrics, 8. 611, 1953

94 THORN, G. W, HARRISON, J H., MERRILL, J. P., CRISCITIELLO, M G, FRAWLEY, T F., and FINKENSTAEDT, J. T. Clinical studies on bilateral complete adrenalectomy in patients with severe hypertensive vascular disease Ann intern. Med., 37. 972, 1952

95 THORPE, J J., WELCH, W J., and POINDEXTER, C A. Bilateral thoracolumbar sympathectomy for hypertension: A study of 500 cases. Amer J Med, 9: 500, 1950

96 TIBBETS, R. W Leucotomy and hypertension. A case report. Brit. med. J, 2 1452, 1949

97 TRUMBLE, H C Sympathectomy in the treatment of high blood pressure — Late results Alfred Hosp clin Rep (Melbourne), 4: 31, 1954.

98 VORIS, H C Thoracolumbar sympathectomy for hypertension Surg. Clin. N Amer, 35. 255, 1955.

99 WEEKS, C, RYAN, B J, and VAN HOY, J M Two deaths associated with supradiaphragmatic vagotomy J Amer med Ass, 132: 988, 1946.

100 WHITE, P D Hypertension heart disease in 1827, 1936 and 1945 Univ. N de Méx, México, 1945 Cited by Chávez, I, and Méndez, L., Amer. Heart J, 37 523, 1949

100a WHITE, P D Severe hyper- card fifty 194

101 WHITE, ... and WILLIAMS, A Follow-up study of one

hundred private hypertensive patients with cardiovascular complications. J. Amer. med. Ass., 143: 1311, 1950.

102 WHITE, P. D., SMITHWICK, R. H., MATHEWS, M. W., and EVANS, E. The electrocardiogram in hypertension. II. The effect of radical lumbodorsal sympathectomy (Preliminary report). Amer. Heart J., 30: 165, 1945.

103 WILKINS, R. W., CULBERTSON, J. W., and HALPERIN, M. H. The hemodynamic effects of sympathectomy in essential hypertension. Ann intern. Med., 30: 291, 1949.

104 WILKINS, R. W., CULBERTSON, J. W., and SMITHWICK, R. H. The effects of various types of sympathectomy upon vasopressor responses in hypertensive patients. Surg. Gynec. Obstet., 87: 661, 1948.

105 WOLFERTH, C. C., JEFFERS, W. A., LUKENS, F. D. W., ZINTEL, H. A., and HAFKENSCHIEL, J. H. Observations on the results of subtotal adrenalectomy in the treatment of severe otherwise intractable hypertension and their bearing on the mechanism by which hypertension is maintained. Ann. intern. Med., 35: 8, 1951.

106 WRIGHT, A. D. The management of patients with essential hypertension. Proc. roy. Soc. Med., 40: 774, 1947.

107 ZINTEL, H. A., MACKIE, J. A., JEFFERS, W. A., WOLFERTH, C. C., HILLS, A. G., SELLERS, A. M., and HAFKENSCHIEL, J. H. Combined adrenalectomy-sympathectomy in the treatment of patients with essential hypertension. Surgery, 34: 438, 1953

108 ZINTEL, H. A., SELLERS, A. M., JEFFERS, W. A., MACKIE, J. A., HAFKENSCHIEL, J. H., and LINDAUER, M. A. A three to seven year postoperative evaluation of 76 patients with severe hypertension treated by thoracolumbar sympathectomy. Surg Gynec. Obstet., 101: 48, 1955a.

109 ZINTEL, H. A., MACKIE, J. A., SELLERS, A. M., JEFFERS, W. A., HAFKENSCHIEL, J. H., and LINDAUER, M. A. Results of thoracolumbar sympathectomy for essential hypertension Arch. Surg. (Chicago), 71: 216, 1955b

110 ZINTEL, H. A., WOLFERTH, C. C., JEFFERS, W. A., HAFKENSCHIEL, J. H., and LUKENS, F. D. W. Subtotal adrenalectomy in the treatment of patients with severe essential hypertension Ann. Surg., 132: 351, 1951

CHAPTER XV

# SEVERE SALT RESTRICTION

— . . . . . that in hypertensive patients

striking character.

The degree of salt restriction necessary to obtain significant improvements and the dietary miseries involved, are such that, in most clinics, few persist in the régime. Great interest attaches, nevertheless, to the effects of salt restriction upon the blood pressure and upon the clinical manifestations in hypertension.

At a time when the relationship between salt retention and oedema was attracting attention, and Achard and Loeper (1901) were speculating about the possibility of "dry" retention of salt in the body, Ambard and Beaujard (1904, 1905) described the use of salt restriction for the treatment of hypertension. A salt-poor diet was also devised by Laufer (1904), very similar to that of Kempner and containing as little as 0.25 gm. of sodium chloride daily. Bayer (1907) also used a salt-poor diet for the treatment of hypertension.

Severe salt restriction was introduced into the United States by Allen (1920) and Allen and Sherrill (1922), and for a check on their régime they estimated the urinary chloride output of their patients. They tried to make the diet tolerable and treated a considerable number of hypertensive patients in this way. Volhard (1931) also reported success with salt restriction.

Criticism was directed against this method of treatment [10, 33, 39, 43], perhaps because some of those who attempted to repeat the work did not adopt a sufficiently meticulous technique, and the use of salt restricted diets declined until Kempner, in 1944, introduced his rice diet, which embodied severe salt restriction and other features which he regards as essential. The work of Kempner has redirected attention to the effects of salt restriction in essential hypertension and has also prompted investigations on metabolic problems.

In essence, Kempner's diet consists of rice, fruit and sugar. It contains 2,000 calories with not more than 5 gm. fat, about 20 gm. protein derived from rice and fruit and not more than 200 mg. chloride and 150 mg sodium. The patient takes 250 to 350 gm of dry rice daily.

hundred private hypertensive patients with cardiovascular complications J. Amer. med. Ass., 143: 1311, 1950.

102 WHITE, P. D., SMITHWICK, R. H., MATHEWS, M. W., and EVANS, E. The electrocardiogram in hypertension. II. The effect of radical lumbodorsal sympathectomy (Preliminary report). Amer. Heart J., 30. 165, 1945.

103 WILKINS, R. W., CULBERTSON, J. W., and HALPERIN, M. H. The hemodynamic effects of sympathectomy in essential hypertension. Ann intern. Med., 30: 291, 1949.

104 WILKINS, R. W., CULBERTSON, J. W., and SMITHWICK, R. H. The effects of various types of sympathectomy upon vasopressor responses in hypertensive patients. Surg. Gynec. Obstet., 87: 661, 1948.

105 WOLFERTH, C. C., JEFFERS, W. A., LUKENS, F. D. W., ZINTEL, H. A, and HAFKENSCHIEL, J. H. *Observations on the results of subtotal adrenalectomy* in the treatment of severe otherwise intractable hypertension and their bearing on the mechanism by which hypertension is maintained. Ann. intern. Med., 35: 8, 1951.

106 WRIGHT, A. D. The management of patients with essential hypertension. Proc. roy. Soc. Med., 40: 774, 1947.

107 ZINTEL, H. A, MACKIE, J. A., JEFFERS, W. A, WOLFERTH, C. C, HILLS, A. G., SELLERS, A. M., and HAFKENSCHIEL, J. H. Combined adrenalectomy-sympathectomy in the treatment of patients with essential hypertension. Surgery, 34: 438, 1953

108 ZINTEL, H. A., SELLERS, A. M., JEFFERS, W A., MACKIE, J. A, HAFKENSCHIEL, J. H., and LINDAUER, M. A A three to seven year postoperative evaluation of 76 patients with severe hypertension treated by thoracolumbar sympathectomy Surg Gynec. Obstet., 101: 48, 1955a.

109 ZINTEL, H. A., MACKIE, J. A., SELLERS, A. M., JEFFERS, W. A, HAFKENSCHIEL, *J. H., and LINDAUER, M A Results of thoracolumbar* sympathectomy for essential hypertension Arch. Surg (Chicago), 71: 215, 1955b.

110 ZINTEL, H. A., WOLFERTH, C. C., JEFFERS, W. A, HAFKENSCHIEL, J. H., and LUKENS, F D W. *Subtotal adrenalectomy in the treatment of* patients with severe essential hypertension Ann. Surg, 132: 351, 1951

conditions imposed. Dole et al. (1950) observed 6 patients with hypertension on a Kempner rice - fruit diet during six months' residence on the metabolic ward of the Rockefeller Foundation Hospital. Significant reductions of the blood pressure were correlated with changes in the sodium intake in 5 out of 6 patients. Watkin et al. (1950) also obtained blood pressure falls under controlled conditions but, as in other series, some of the patients failed to show any reduction. The results of the Medical Research Council of Great Britain were very similar. Additions of salt in capsules removed the hypotensive action of the régime.

Hatch et al. (1954) made a four year investigation of the effect of the Kempner rice diet. They tried the effects of modifying the diet by adding low sodium protein, fat or vegetables, or a combination of these. The falls of blood pressure evidently depended on sodium deprivation. They found that the addition of ½ gm. sodium chloride per day in tablet form to the salt-poor diet did not usually elevate the blood pressure, but the addition of 3 gm. per day prevented the lowering of the blood pressure.

Chasis et al. (1949), in a closely controlled study, found the blood pressure level reductions on the rice diet were not significant in view of the large spontaneous variations. Leaving aside the question of statistical significance, their data do show some slight blood pressure reductions during consumption of the rice diet, and in some patients a rise of blood pressure when salt is restored.

The manner in which salt restriction reduces the blood pressure of some hypertensive patients is unknown, but among the suggestions offered are:

1. That it is due to decrease in the volume of plasma and of extracellular fluid.
2. That there is some effect upon the secretion of the adrenal cortex.
3. That there is an effect on the reactivity of blood vessels.

The observation of Fatt and Katz (1952) may be relevant to this problem, they state that marked sodium deficiency gives rise to neuromuscular block and a reduced output of acetyl choline, but it is not clear whether anything of this kind happens with the degrees of sodium deficiency which we encounter clinically.

Curtailment of the salt intake leads to loss of salt reserves amounting, as an average in the course of four to six weeks, to about 170 mEq. of sodium and 240 mEq. of chloride, according to Hatch (1954). This depletion was associated with a blood pressure fall of 22 mm. Hg systolic and 12 mm. Hg diastolic. Dole et al. (1951) found a loss of 400 to 700 mEq of sodium on their régime.

It is of interest that, despite the loss of salt, the composition of the serum is not altered much. Watkin et al. (1950) found the changes

It is boiled or steamed in plain water or fruit juice and, if the water contains more sodium than 20 mg. per litre, distilled water is used. Various precautions are mentioned as to the sources of fruit juice. White sugar and dextrose are taken quite freely. Tomato and vegetable juices are not allowed and supplementary vitamins are added, namely: vitamin A, 5,000 u., vitamin D, 1,000 u., thiamine chloride, 5 mg., riboflavine, 5 mg., nicotinamide, 25 mg., and calcium pantothenate, 2 mg.

This diet has the great advantage of simplicity. It is easy to prescribe and its restrictive nature makes it easy to understand if difficult to tolerate. At a later stage certain specified additions to the dietary may be allowed, provided they do not increase the salt intake and are not associated with any increase in the blood pressure.

## PHYSIOLOGICAL EFFECTS OF SALT RESTRICTION

### *Effects on the Blood Pressure*

Early uncertainties concerning the effects of salt restriction in hypertension depended to some extent upon the fact that there is an important difference in the effects of sodium restriction to 1 gm. as sodium chloride per day, and patients who are restricted to 0 4 gm. of sodium chloride or less per day. Furthermore, many patients on salt restriction make dietary errors or take liberties, and estimates of the urinary excretion of sodium are necessary for proper control over the régime. It is necessary also to distinguish between the blood pressure falls which occur even with placebos and falls of pressure due specifically to the therapy. When very large falls of blood pressure are obtained regularly the decision is easy, but in the case of salt restriction the blood pressure falls are sometimes small, say 20/8 mm. Hg, and not all patients respond.

In recent years much has been done to clarify these problems. It is certainly true that when the blood pressures during severe salt restriction are compared with the blood pressures during a similar régime, but with salt added in capsules, the extent of the fall of blood pressure attributable to salt restriction is often small, but in individual cases considerable. Such an investigation was made by Grollman et al (1945), who obtained quite definite falls of blood pressure in some patients. They then showed that if, while otherwise continuing with the diet, salt was added, the blood pressure rose again. They concluded that salt restricted diets must be extremely rigid in order to produce their effects and that they were worth a trial in hypertension, the diet being continued in those patients who responded adequately.

Landowne et al. (1949) made a similar investigation and found a difference from the controls of only 8 7 mm. Hg systolic and 4.7 mm. Hg diastolic in 8 subjects who complied with the strictly controlled

expressed in mEq/l., to be of the order of —3.0 sodium, +0.3 potassium, —7.6 chloride, +4.6 bicarbonate. There would be no difficulty in explaining loss of sodium without much change in the serum composition if a considerable decrease were demonstrated in the extracellular fluid volume, including the plasma volume.

### The Plasma Volume

As an index of the plasma volume, Watkin et al. (1950) used dilution of the dye Evan's blue (T-1824). In hypertensive heart failure they found that the plasma volume was much increased above the normal, namely, of the order of 4,030 ml., and it was reduced by as much as 20.3 per cent on treatment with the rice diet. The average of all their hypertensive cases, mostly not in heart failure, gave a smaller reduction in the plasma volume, averaging 9 per cent. No definite correlation was noted between the extent of the blood pressure fall and the plasma volume. Dole et al. (1950) also found no important change in the plasma volume, though it appears from their data that it was somewhat lower on the rice diet than afterwards, when salt had been restored. Currens et al. (1951) found the plasma volume showed no significant change in 3 patients and a significant decrease in 3 patients. Murphy (1950) found decreases of plasma volume, as did O'Donnell (1955) after salt deprivation for periods of 10 to 20 days.

### The Extracellular Fluid Volume

There seems to be some doubt also concerning the effect of salt restriction on the volume of the extracellular fluid. McCance (1938) found an appreciable decrease in the extracellular fluid volume following salt deprivation. Watkin et al. (1950), using the thiocyanate method, found that the rice diet led to a reduction in the extracellular fluid volume to about 85 per cent of the original level; they included some heart failure cases in their series. Murphy (1950) also found highly significant decreases of the thiocyanate (extracellular) space and did not include heart failure cases. Dole et al. (1950) reported no depletion of the extracellular water. Currens et al. (1951) found the thiocyanate space (other than the plasma volume) decreased in two patients and not decreased significantly in four patients.

According to Watkin et al. (1950) the antipyrine space is diminished after a rice diet, the total body water being reduced from 53.3 to 48.7 per cent of the body weight in hypertensive patients who were not in congestive heart failure.

The observations of my colleague, Dr. O'Donnell, seem to throw some light on the mode of action of salt-poor diets and may, in part, explain some of the variations in the circulatory effects in hypertension Periods of rigid salt restriction of 10 to 20 days' duration were not regularly associated with any substantial fall in blood pressure in the

supine p[illegible]
sion, an[illegible]
[illegible] that salt restriction caused enhanced reactivity to the hypotensive action of hexamethonium. When the blood volume was determined by the Evan's blue method it was found to be reduced in most, but not in all, instances. There proved to be a correlation between the decrease in the plasma volume so estimated and the occurrence of postural hypotension; and also between decrease in plasma volume and enhancement of the postural hypotension induced by hexamethonium (Table XV 1).

TABLE XV 1. *Effect of Salt-Free Diet*
(Personal communication, Dr. T. V. O'Donnell)

| Patient | Plasma volume change ml | Occurrence of a postural B P fall on salt-free diet | Enhancement of postural hypotension induced by hexamethonium |
|---|---|---|---|
| Mrs Cl. | — 880 | Present | Increase |
| Mr. D. | — 845 | Present | Not tested |
| Mrs Ch. | — 804 | Present | Not tested |
| Mrs Cu | — 747 | Present | Not tested |
| Mrs. W | — 700 | Absent | Increase |
| Miss E | — 600 | Present | Increase |
| Mrs M | — 300 | Present | Increase |
| Mr. F. | — 290 | Absent | Increase |
| Miss P | — 145 | Absent | Increase |
| Mrs Ca | No change | Absent | None |
| Mrs A. | + 200 | Absent | None |
| Mrs W | + 400 | Absent | None |

O'Donnell also found that postural hypotension occurred after venesection, and this manifestation was removed if a blood transfusion or an infusion of dextran was administered. Similarly, the postural hypotension induced by salt restriction was removed following an infusion of salt-free dextran solution. Administration of salt-free dextran solution or of a blood transfusion also diminished the responsiveness to the hypotensive action of ganglion blocking agents. My impression is that results such as these are due, in part, to the fact that reduction in the blood volume calls for increase in the activity of sympathetic regulatory reflexes, thereby decreasing the potentiality for further increase in sympathetic activity. If then some further demand is made upon the sympathetic nervous system, *for example* by assumption of the erect posture, then postural hypotension may occur as an indication of sympathetic unresponsiveness.

When a blood transfusion is given, or the blood volume is increased above the normal by dextran solution, the regulatory processes act in

expressed in mEq/l., to be of the order of —3.0 sodium, +0.3 potassium, —7.6 chloride, +4.6 bicarbonate. There would be no difficulty in explaining loss of sodium without much change in the serum composition if a considerable decrease were demonstrated in the extracellular fluid volume, including the plasma volume.

### The Plasma Volume

As an index of the plasma volume, Watkin et al. (1950) used dilution of the dye Evan's blue (T-1824). In hypertensive heart failure they found that the plasma volume was much increased above the normal, namely, of the order of 4,030 ml., and it was reduced by as much as 20.3 per cent on treatment with the rice diet. The average of all their hypertensive cases, mostly not in heart failure, gave a smaller reduction in the plasma volume, averaging 9 per cent. No definite correlation was noted between the extent of the blood pressure fall and the plasma volume. Dole et al. (1950) also found no important change in the plasma volume, though it appears from their data that it was somewhat lower on the rice diet than afterwards, when salt had been restored. Currens et al. (1951) found the plasma volume showed no significant change in 3 patients and a significant decrease in 3 patients. Murphy (1950) found decreases of plasma volume, as did O'Donnell (1955) after salt deprivation for periods of 10 to 20 days.

### The Extracellular Fluid Volume

There seems to be some doubt also concerning the effect of salt restriction on the volume of the extracellular fluid. McCance (1938) found an appreciable decrease in the extracellular fluid volume following salt deprivation. Watkin et al. (1950), using the thiocyanate method, found that the rice diet led to a reduction in the extracellular fluid volume to about 85 per cent of the original level; they included some heart failure cases in their series. Murphy (1950) also found highly significant decreases of the thiocyanate (extracellular) space and did not include heart failure cases. Dole et al. (1950) reported no depletion of the extracellular water. Currens et al. (1951) found the thiocyanate space (other than the plasma volume) decreased in two patients and not decreased significantly in four patients.

According to Watkin et al. (1950) the antipyrine space is diminished after a rice diet, the total body water being reduced from 53.3 to 48.7 per cent of the body weight in hypertensive patients who were not in congestive heart failure.

The observations of my colleague, Dr. O'Donnell, seem to throw some light on the mode of action of salt-poor diets and may, in part, explain some of the variations in the circulatory effects in hypertension Periods of rigid salt restriction of 10 to 20 days' duration were not regularly associated with any substantial fall in blood pressure in the

Peschel and Lohmann-Peschel (1952) find that, in the absence of renal disease, an equilibrium is reached after five weeks of the dietary régime, after which no further important change takes place, and patients are able to maintain a state of equilibrium. About 5 per cent of [illegible] without renal disease develop a low sodium syndrome and [illegible] of chloride

[illegible]

if a disturbance seems to be pending. Dole et al. (1950) made a careful metabolic study of 6 patients on a rice - fruit diet. They stated that for a few months at least sodium balance was maintained, but one patient with chronic nephritis seemed to lose more sodium than other patients and her serum sodium fell from 144 mEq/l. to 129 mEq/l. The British Medical Research Council Report (1950) makes reference

[illegible]

had a rise of blood urea from 48 to 186 mg per cent. My impression is that patients with substantial renal disease may be precipitated into uraemia as the result of severe salt restriction. Furthermore, the kidneys may be unable to conserve sufficient sodium and dangerous loss of base may occur. This risk is only to be avoided by the exercise of great skill and meticulous supervision.

Hatch (1954) refers to the changes in electrolytes in 11 patients on rigid salt restriction The average values for the control observations, expressed in mEq/l., were 140 sodium, 4.4 potassium, 105 chloride. The average blood pressure corresponding was 212/121 mm. Hg. After five weeks' rice diet the sodium was 137, potassium, 4.6, chloride 99. The average blood pressure was 190/109 mm Hg. Hatch found that the total loss of sodiu[illegible]
mEq Watkin et a[illegible]
mEq/l before an[illegible]
before to 4.6, chl[illegible]
27 6 mEq/l. before to 32 2 on the rice diet.

Evidently there is no great change in the electrolyte composition of the plasma

## Effect of Severe Salt Restriction on Renal Function

The effect of a Kempner rice diet or of severe salt restriction upon the renal function is of great interest. A decrease in the glomerular filtration rate, and usually of the renal plasma flow, has been noted by several observers[13, 14, 16, 67, 68].

Baldes and Smirk (1934) found that during severe salt restriction

the opposite direction, the sympathetic discharge to blood vessels being thereby decreased somewhat below their normal. Under these conditions, with unexpended reserves of sympathetic activity, the body is in a better position to combat changes which call for additional sympathetic action.

It appears that in certain patients, the plasma volume is reduced by salt deprivation and this is probably one of the factors in the production of spontaneous postural hypotension, in potentiating the action of hexamethonium, and perhaps in reducing the supine blood pressure. Probably severe salt deprivation creates a need for increase in sympathetic activity whenever it reduces the plasma and the extracellular fluid volumes. Blood pressure falls will only occur, however, in those patients whose regulatory mechanisms fail to respond adequately to a demand for increase in sympathetic activity. Sometimes it is only when assumption of the standing posture increases the demand for additional sympathetic activity that inadequacy of the sympathetic response is revealed. We observed some analogous occurrences in the course of experiments with hypotensive and hypertensive drugs (Chapter XVIII).

### Effect of the Kempner Rice Diet on Cardiac Output

The effects of the rice diet on the cardiac output were studied by Watkin et al. (1950) using cardiac catheterization. They find that favourable responses are not associated with a significant decline in the cardiac output but are associated with a decrease in the peripheral resistance.

### Changes of Blood Composition on the Rice Diet

Peschel and Lohmann-Peschel (1952), of Kempner's clinic, have published an account of the electrolyte changes in the blood in 80 patients with hypertensive vascular disease on the Kempner rice diet The figures are averages and represent mEq/l.

| | Control | After ten weeks' rice diet |
|---|---|---|
| Sodium | 145.0 ± 4 1 | 142.3 ± 4.8 |
| Potassium | 4 9 ± 0.5 | 5.4 ± 0 6 |
| Total base | 157.6 ± 4 1 | 154.0 ± 4.6 |
| Chloride | 100.7 ± 3 0 | 94.3 ± 4.9 |
| Bicarbonate | 31.2 ± 1.8 | 34.5 ± 2.4 |

Consistent with these findings is the observation of Baldes and Smirk (1934) that, on a salt-poor diet containing less than 0.17 gm. of sodium daily, the total (crystalloidal) osmotic pressure in three normal human subjects fell by the osmotic equivalent of 0.027 per cent sodium chloride.

Peschel and Lohmann-Peschel (1952) find that, in the absence of renal disease, an equilibrium is reached after five weeks of the dietary [illegible] change takes place, and [illegible]

[illegible] such as 117.4 mEq/l. of sodium [illegible] They mention the [illegible]

especially in patients with impaired renal function [illegible] a strict rice diet can be given to such patients, but checks of the serum electrolytes must be made at least twice weekly, and more frequently if a disturbance seems to be pending. Dole et al. (1950) made a careful metabolic study of 6 patients on a rice - fruit diet. They stated that for a few months at least sodium balance was maintained, but one patient with chronic nephritis seemed to lose more sodium than other patients and her serum sodium fell from 144 mEq/l. to 129 mEq/l. The British Medical Research Council Report (1950) makes reference to two patients with impaired renal function who continued to excrete sodium in the urine on a rice diet; one died from uraemia and one other had a rise of blood urea from 48 to 186 mg per cent. My impression is that patients with substantial renal disease may be precipitated into uraemia as the result of severe salt restriction. Furthermore, the kidneys may be unable to conserve sufficient sodium and dangerous loss of base may occur. This risk is only to be avoided by the exercise of great skill and meticulous supervision.

Hatch (1954) refers to the changes in electrolytes in 11 patients on [illegible] five weeks' rice diet the sodium was 137, potassium, 4.6, chloride 99. The average blood pressure was 190/109 mm. Hg. Hatch found that the [illegible] 27.6 mEq/l. before to 32.2 on the rice diet.

Evidently there is no great change in the electrolyte composition of the plasma.

## Effect of Severe Salt Restriction on Renal Function

The effect of a Kempner rice diet or of severe salt restriction upon the renal function is of great interest. A decrease in the glomerular filtration rate, and usually of the renal plasma flow, has been noted by several observers [13, 14, 16, 57, 58].

Baldes and Smirk (1934) found that during severe salt restriction

the diuresis following the administration of 1 litre of water was diminished appreciably. Black, Platt and Stanbury (1950 a, b) noted that following a period of salt restriction there is a change in the action of the renal tubules in that, with the same or even with an enhanced sodium load, the sodium was reabsorbed to a greater extent than normal. In other words, the renal tubule cells appear to have been conditioned to reabsorb sodium more actively.

*A corresponding observation was made by Hatch (1954) who found* that, in patients who have had severe salt restriction, the addition to the diet of 8.5 or 17 mEq. sodium chloride a day in 4 patients led, quite soon, to the appearance of chloride ion in the urine, but none of the additional sodium ion was excreted in the urine for at least four weeks.

Hatch (1954) cites a personal communication from Genest who examined the urine for steroids and was unable to find any significant alterations related to the sodium intake. London and Terry (1952) also sought for evidence of a defect in the adrenal cortex control of salt metabolism in essential hypertension and applied the Soffer test. The Soffer test consists of a salt loading test carried out first under control conditions, and subsequently after the patient has received an injection of desoxycorticosterone. The patients with hypertension showed a normal response and failed to demonstrate any electrolyte abnormality of the type encountered in Cushing's syndrome. Other evidence that there is usually no gross change in the adrenal cortex in hypertension comes from the finding of 17 ketosteriods and 11 oxysteroids in low or normal amounts in the urine of hypertensive patients. (But see Chapter VI — aldosteronism). Recently Goldman et al. (1956) have described histological changes in the adrenal cortex of the rat on salt restriction and return towards normal on restoring salt.

It is of interest to refer at this stage to some peculiar differences in the salt metabolism of hypertensives and normotensives.

### *Salt Metabolism in Essential Hypertension and in Normotension*

The levels of the serum sodium and chloride are well within normal limits in essential hypertension and the blood volume is also normal It seems, therefore, that no difference between the extracellular sodium metabolism of hypertensives and normotensives has been discovered which could offer an easy explanation of the differences in the blood pressure. Nevertheless, there are changes in the sodium metabolism.

Allen and Sherrill (1922) found that on salt restriction diets hypertensives conserve their salt reserves better than the normotensives; and Pines and Perera (1949) remark that hypertensives withstand

significantly greater in normals than in hypertensives. Selye (1947) states that in hypertensive patients the ratio of sodium to chloride is usually higher than in normotensives. Green et al. (1954) studied the effect of administering saline intravenously to hypertensive patients. They thought that hypertensives could be separated into groups of high salt-excretors and normal salt-excretors. The high salt-excretors had an increased output of [illegible] water under basal conditions and an increased appetite for s[illegible]

[illegible]

hypertension might be the result of haemodynamic changes [illegible] with the hypertension and involving the kidneys, and possibly the volume of fluid stored in the extracellular compartment.

A slight increase in capillary pressure in hypertension might lead to an increase in the amount of fluid held extracellularly.

## Nitrogen Balance on the Kempner Diet

The Kempner rice diet has approximately 20 gm. of protein derived from rice and fruit, and the question of whether nitrogen balance can be maintained on this has been investigated by several groups. Kempner (1948) and Peschel and Lohmann-Peschel (1950) find that nitrogen equilibrium is maintained. They reported decreases in the blood non-protein nitrogen. Schwartz and Merlis (1948) found that there was a negative protein balance but, for most of their patients, the period of observation was short. Currens et al. (1951) noted that the nitrogen balance was negative soon after instituting the diet, but the loss diminished to a remarkable extent after three to six months. Three patients investigated by the British Medical Research Council (1950) were in negative balance at the end of six weeks. This group also noted that original negative balances gradually became less pronounced. Watkin et al (1950) also found a negative nitrogen balance in some of their patients and this was combated by the addition of lonalac (a salt-free source of milk protein). Watkin et al. think that sooner or later the rice diet should be supplemented by a source of protein other than rice. In some instances patients find it very difficult to consume all the rice with which they are provided and a negative nitrogen balance may be the result of this.

Despite this conflict of opinion about nitrogen balance, one thing has been made clear, namely, that even if in some instances the nitrogen balance is negative on a Kempner rice diet observed faithfully, the negativity is slight and balance can be restored by the addition of small amounts of protein. Diets with a very low sodium content can be

arranged without deprivation of protein [29] and their effects on the blood pressure appear to resemble the effects of the Kempner diet. Carbohydrate [29], fat [29] and ammonium chloride [20] can be also added to the diet without raising the blood pressure, provided there is no increase in the amount of sodium.

### Effect of the Kempner Rice Diet on Cholesterol Metabolism

Although decreases in blood pressure appear to depend to a large extent on salt restriction, there are features of the Kempner diet which may be important in other respects; in particular, the low content of fat and cholesterol may influence the future prospects of patients with a disposition to arteriosclerosis. Kempner (1949) and Watkin et al. (1950) make reference to the decrease in blood cholesterol, especially in the cholesterol esters (Starke, 1950). Watkin et al. (1950) also find that there is a decline in the cholesterol/phospholipid ratio.

As yet it has not been fully demonstrated in man that the development of arteriosclerosis depends upon the level of the blood cholesterol, but there is much evidence that low fat diets reduce the incidence of arteriosclerosis (Chapter X).

## TREATMENT OF HYPERTENSION BY SEVERE SALT RESTRICTION

Salt restricted diets have been in use for hypertension since the publications of Ambard and Beaujard in 1904. Allen in 1920, in the United States, advocated strict salt restriction and has since strongly maintained the efficiency of his régime, and that salt is the only necessary restriction. In discussions on hypertension therapy at scientific meetings he has made it clear that he regards rice as a redundant and unappetising addition to his saltless régime. Kempner was led to use the rice diet as the result of experiments on kidney tissue slices which led him to consider that a metabolic overload, applied to kidneys with deficient oxygenation, might lead to the release of renal pressor substances, thereby causing hypertension. His early observations are set out in a paper published in 1944 [30] and his experiences later have been reviewed in 1948 and 1955 [31, 41].

The early observations of Allen and of Kempner on blood pressure changes were not rigidly controlled, but their evidence of the reversal of certain clinical manifestations was impressive, and the experience of later investigators underlines the fact that great clinical skill was needed to obtain and maintain results. Unfortunately, the rice diet is distasteful to a considerable majority of patients, and is so revolting to some that they are unable to continue.

Confirmation of many of Kempner's results have been published by Behrendt and Burgess (1947), Flipse and Flipse (1947), Rosenberg et al.

(1948), Contratto and Rogers (1948), Lichtwitz et al. (1950), as well as others quoted in the previous section. In the report of the Medical Re- [illegible] based on 33 patients with symptoms [illegible]

[illegible]

per cent of the [illegible]

and was accompanied often by great symptomatic relief. They noted, however, that the régime was very difficult to adhere to and as soon as the sodium content rose a little the blood pressure increased again. They did not recommend the rice diet as a practicable *method for the routine therapy of hypertension.*

Pines and Perera (1949) agreed that the blood pressure levels may be at least slightly modified by extremes of restriction or addition of sodium to the diet and they felt that such diets deserved a clinical trial but were not appropriate for routine therapy.

Although Currens et al. (1951) found rather striking improvements in the blood pressure level in some patients, they considered that, in general, the diet was of limited value therapeutically. A proportion of patients responded in the series of Dock (1946).

The conclusion of Watkin et al. (1950) was that the Kempner régime imposes such hardship on the patient that control is extremely difficult. In renal cases there may be unfavourable, even dangerous, reactions with retention *of nitrogen, sometimes uraemia and death.* Kempner himself has strongly emphasized the need for a close laboratory control.

Schroeder et al. (1949) found a group of 6 female patients among 22 patients with hypertension who exhibited a "pseudo-Cushing's syndrome". In these patients restriction of salt appeared to have a more substantial effect than in their other patients, whose falls of blood pressure were unimpressive; but Landowne et al. (1949) stated that in their series they were unable to identify a "pseudo-Cushing's" group of patients with this characteristic

## Ion Exchange Resins

Ion exchange resins have been used to increase the elimination of sodium from the body and supplement the effect of salt restriction. Gill and Duncan (1952) reported their experience on 38 ambulatory patients using a commercial cation exchange resin, Resodec. They advise that the 24-hour urine sodium should be reduced to 0.5 gm. or less and that a two months' *period of observation* is needed to decide the efficacy of the régime. Their observations were controlled by placebos and salt additions. They obtained diastolic pressure decreases of 20 mm or more in 15 out of 38 cases. Observations by Leroy Duncan (1953) confirm the efficacy of cation exchange resins in the removal of sodium. In a few patients on salt restriction we have made

use of ion exchange resins; and to supplement the effects of salt restriction we have allowed the administration of an ion exchange resin on three days a week. In one patient who has maintained rigid salt restriction for a period of six years, except when he has to travel away from home, ion exchange resins have enabled him to minimize the effect of the increased sodium intake when he travels. Daily administration of ion exchange resins over long periods are apt to lead to electrolyte disturbances other than sodium withdrawal, but their intermittent use seems to require a less close supervision of the patient.

## Relief of Clinical Manifestations

Certain clinical improvements are well known to occur with salt restriction and the question arises whether these are induced by the intermediation of blood pressure lowering or in some other way. For example, great improvement in congestive heart failure may be anticipated with adequate salt restriction, but this effect is obtained in normotensive as well as in hypertensive heart failure.

Decreases in heart size have been noted by Kempner (1948), Dole et al. (1950), Watkin et al. (1950), the British Medical Research Council (1950) and Hatch et al. (1954). Electrocardiographic improvements such as the return of positive T waves, return of ST segments to the isoelectric line, and decrease in the height of the R waves in left ventricular leads, have been reported in papers by Kempner (1948), Dole et al. (1950), Watkin et al. (1950), and Hatch et al. (1954).

Kempner (1948) has published some beautiful retinal photographs illustrating the disappearance of exudative changes on the rice diet, and improvements have been noted by Allen (1949), Dole et al. (1950), Watkin et al. (1950), Gill and Duncan (1952) and Hatch et al. (1954). The changes include the disappearance of papilloedema as well as of retinal exudates and haemorrhages. The question arises whether the retinal improvements are due to decrease in the blood pressure or to the effect of electrolyte changes upon the retinal tissues or, more probably, to a combination of these. It is of interest that Dole et al. (1950) noted much retinal improvement in a patient with little fall in blood pressure.

Fishberg (1954) makes the comment that few patients remain on the unmodified rice diet for a long period of time and that in many instances food becomes repugnant. There is severe limitation of working capacity, but a few patients can pursue a light occupation while on a rice diet with only slight additions. He considers that the rice diet should not be used in patients with nitrogen retention, or if the maximum urinary specific gravity is less than 1.015. He finds that the rice diet has no advantage, so far as concerns blood pressure control, over a more liberal diet containing 200 mg. of sodium per 24 hours.

Diets such as those containing *2 or 3 gm. of* sodium daily are only of value in respect of heart failure.

Newborg and Kempner (1955) gave an analysis of their results in 153 malignant hypertension patients (with papilloedema) who attempted the rice diet. Of these, 33 had *difficulties with the electrolyte* balance and additional sodium chloride had to be added to the régime. All of these 33 patients died. Of the remaining 120 patients several maintained a satisfactory régime for a period of time, and then more or less went off the diet. There was a higher proportion of deaths among those who [illegible] maintain the diet strictly. Of the 120 patients 30 had died at th[illegible]
68 had die[illegible]
101 were [illegible]
a majority of the living ones having remained on the rice diet. Kempner made a study of 100 patients selected out of the 120 who had been followed in greater detail. The 100 patients included all the living cases [illegible]

[illegible]

better expect[illegible] *of the palliative era.* Of the 100 selected patients, 52 remained alive about four years after treatment began. Of these, 15 patients had had the rice diet alone for an average of 15 months and had had drug therapy in addition for a further period of 15 months. In the 100 patients, all with papilloedema, the papilloedema had disappeared in 92 patients in an average of five months. It partially disappeared in 3 patients in two months and there was no change in 5 patients in four months. Haemorrhages and exudates also decreased.

## Comment

While there seems to be not the slightest doubt that the course of malignant hypertension, and of less severe types, can be substantially improved by the rice diet, and also by equivalent régimes of sodium restriction, the observations of Kempner, as well as those of many other writers, indicate how large a proportion of patients are unable to continue the régime for one reason or another. It would, I think, be generally assumed that few clinics could maintain as high a *proportion* on treatment as Kempner has succeeded in doing.

My experience with the rice diet and severe salt restriction has been *limited.* I have seen a number of patients who had falls of blood pressure which were well outside the placebo range and who had clinical improvement. A few patients in my experience have *become well* adapted, especially those who have had considerable clinical improvement. To some of these patients normally salted foods, taken inadvertently, are much too strongly flavoured. Patients have commented to

me on their great sensitivity to the taste of salt, their own saliva sometimes having a salty flavour.

I feel that the

at the conclusion (

by salt restriction. He quotes from Alice in Wonderland where the White King said, "There's nothing like eating hay when you're feeling faint . . ."

"I didn't say there was nothing better", the King replied, "I just said there was nothing like it."

## References


1 Achard, C. and Loeper, M. Sur la rétention des chlorures dans les tissus au cours de certains états morbides. C. R Soc Biol. (Paris), **53**: 346, 1901.

2 Allen, F. M. Arterial hypertension. J. Amer. med. Ass, **74**: 652, 1920

3 Allen, F. M Low sodium chloride diets in hypertension — Effects on blood pressure (Report of a discussion). J. Amer. med. Ass., **140**: 462, 1949.

4 Allen, F. M., and Sherrill, J. W The treatment of arterial hypertension J. metab Res., **2**: 429, 1922.

5 Ambard, L., and Beaujard, E. Causes de l'hypertension artérielle. Arch. gén. Méd., **1**: 520, 1904.

6 Ambard, L., and Beaujard, E. La rétention chlorurée sèche. Sem. méd (Paris), **25**: 133, 1905.

7 Baldes, E. J., and Smirk, F. H. The effect of water drinking, mineral starvation and salt administration on the total osmotic pressure of the blood in man, chiefly in relation to the problems of water absorption and water diuresis. J. Physiol. (Lond.), **82**: 62, 1934

8 Bayer, R Ueber den Einfluss des Kochsalzes auf die Arteriosklerotische Hypertonie. Arch. exp. Path Pharmak, **57**. 162, 1907.

9 Behrendt, F., and Burgess, A M Treatment of hypertension with rice diet. R. I. med J, **30**· 25, 1947.

10 Berger, S. S, and Fineberg, M. H The effect of sodium chloride on hypertension. Arch. intern. Med., **44**: 531, 1929

11 Black, D. A. K., Platt, R, and Stanbury, S W Change in kidney tubule functions on a diet poor in sodium chloride Nature (Lond), **165**: 605, 1950a.

12 Black, D. A K, Platt, R., and Stanbury, S W. Regulation of sodium excretion in normal and salt-depleted subjects. Clin. Sci., **9**. 205, 1950b.

13 British Medical Research Council (Cameron, D. R, Dunlop, D M., Platt, R., Rosenheim, M. L, and Sharpey-Schafer, E. P) The rice diet in the treatment of hypertension — A report to the Medical Research Council. Lancet, **2**: 509, 1950.

14 Chasis, H., Goldring, W., Breed, E S., Schreiner, G., and Bolomey, A. Salt and protein restriction, effects on blood pressure and renal hemodynamics in hypertensive patients J. Amer med Ass, **142** 711, 1950.

15 Contratto, A. W., and Rogers, M B The use of the rice diet in the treatment of hypertension in nonhospitalized patients. New Engl. J Med, **239**: 531, 1948

16 Currens, J. H., Reid, E A. S., MacLachlan, E A., and Simeone, F A. Metabolic effects of the rice diet in the treatment of hypertension. New Engl. J. Med, **245**: 354, 1951

17 DAWSON, A. M. The dietary treatment of hypertension. Med. Press, 228: 509, 1952.
18 DOCK, W. Sodium depletion as a therapeutic procedure: The value of ion-exchange resins in withdrawing sodium from the body. Trans. Ass. Amer. Phys., 59: 293, 1946.
19 DOLE, V. P., DAHL, L. K., COTZIAS, G. C., DZIEWIATKOWSKI, D. D., and HARRIS, C. Dietary treatment of hypertension. II. Sodium depletion as related to the therapeutic effect. J. clin. Invest., 30: 584, 1951.
20 DOLE, V. P., DAHL, L. K., COTZIAS, G. C., EDER, H. A., and KREBS, M. E. Dietary treatment of hypertension: Clinical and metabolic studies of patients on the rice-fruit diet. J. clin. Invest., 29: 1189, 1950.
21 DUNCAN, L. E. Effect of edema and dietary sodium on efficacy of sodium removal by cation exchange resin. Amer. Heart J., 45: 802, 1953.
22 FATT, P., and KATZ, B. The effect of sodium ions on neuromuscular transmission. J. Physiol. (Lond.), 118: 73, 1952.
23 FISHBERG, A. M. Hypertension and nephritis. Lea and Febiger, Philadelphia 1954
24 FLIPSE, M. E., and FLIPSE, M. J.
with rice-fruit diet. Sth. M
25 GILL, R. J., and DUNCAN, G. G.
effect of cation-exchange resins. New Engl. J. Med., 247: 271, 1952.
25a GOLDMAN, M. L., RONZONI, E., and SCHROEDER, H. A. The response of the adrenal cortex of the rat to dietary salt restriction and replacement. Endocrinology, 58: 57, 1956
26 GREEN, D. M., JOHNSON, A. D., BRIDGES, W. C., and LEHMANN, J. H. Stages of salt exchange in essential hypertension. Circulation (N.Y.), 9: 416, 1954.
27 GROLLMAN, A., HARRISON, T. R., MASON, M. F., BAXTER, J., CRAMPTON, J., and REICHSMAN, F. Sodium restriction in the diet for hypertension. J. Amer. med. Ass., 129: 533, 1945
28 HATCH, F. T. Effects of withdrawal and restoration of dietary sodium chloride upon urinary electrolytes in patients with hypertension. Metabolism, 3: 160, 1954
29 HATCH, F. T., WERTHEIM, A. R., EURMAN, G. H., WATKIN, D. M., FROEB, H. F., and EPSTEIN, H. A. Effects of diet in essential hypertension. III. Alterations in sodium chloride, protein and fat intake. Amer. J. Med., 17: 499, 1954.
30 KEMPNER, W. Treatment of kidney disease and hypertensive vascular
31 KEM
32 KEM
and arteriosclerotic vascular disease with the rice diet. Ann. intern. Med., 31: 821, 1949
33 LANDOWNE, M., THOMPSON, W. S., Jr., and RUBY, B. The minimal sodium diet. A controlled study of its effect upon the blood pressure of ambulatory hypertensive subjects. J. Lab. clin. Med., 34: 1380, 1949.
34 LAUFER, R. J. La tension artérielle et la pathogénie de l'oedème: Le régime hydrique et hypochloruré dans les néphrites. C. R. Soc. Biol. (Paris), 56: 249, 1904
35 LICHTWITZ, A., BERTHIER, G., DELAVILLE, M., and THOMOPOULO, H. Le régime de Kempner, technique — indications — résultats. Sem. Hôp. Paris, 26: 256, 1950
36 LONDON, F., and TERRY, L. L. The Soffer test in essential hypertension. J. clin. Invest., 31: 61, 1952.

37 McCANCE, R. A. The effect of salt deficiency in man on the volume of the extracellular fluids, and on the composition of sweat, saliva, gastric juice and cerebrospinal fluid. J. Physiol. (Lond.), 92: 208, 1938.
38 McLESTER, J. S. The influence of rigid salt restriction in the diet of chronic nephritis. Amer. J. med. Sci., 163: 794, 1922.
39 MOSENTHAL, H. O. The treatment of high blood pressure Med. Clin N. Amer., 5: 1139, 1922.
40 MURPHY, R. J. F. The effect of "rice diet" on plasma volume and extracellular fluid space in hypertensive subjects. J. clin. Invest., 29: 912, 1950.
41 NEWBORG, B., and KEMPNER, W. Analysis of 177 cases of hypertensive vascular disease with papilledema — One hundred twenty-six patients treated with rice diet. Amer. J Med, 19: 33, 1955.
42 O'DONNELL, T. V. Variations in postural hypotension with changes in blood volume. Proc. Univ. Otago med. Sch., 33. 36, 1955.
43 O'HARE, J. P., and WALKER, W. G. Observations on salt in vascular hypertension. Arch intern. Med, 32: 283, 1923.
44 PERERA, G. A., and BLOOD, D. W. Disturbance in salt and water metabolism in hypertension. Amer. J. Med., 1: 602, 1946
45 PESCHEL, E., and LOHMANN-PESCHEL, R. Nitrogen balance on rice diet. J. clin. Invest., 29: 455, 1950.
46 PESCHEL, E., and LOHMANN-PESCHEL, R. Electrolyte metabolism during rice diet. I. Serum electrolytes in hypertensive patients without evidence of advanced renal involvement. Arch intern. Med, 89: 234, 1952.
47 PINES, K. L., and PERERA, G A. Sodium chloride restriction in hypertensive vascular disease. Med. Clin. N. Amer, 33: 713, 1949.
48 RESTALL, P A, and SMIRK, F. H. The treatment of high blood pressure with hexamethonium iodide N.Z. med J., 49: 206, 1950
49 ROSENBERG, B., ROSENTHAL, A. E., and ROSENBLUTH, M B. Effect of the low sodium diet and the rice diet on arterial blood pressure. Amer. J. Med, 5: 815, 1948.
50 SCHROEDER, H. A., GOLDMAN, M L, FUTCHER, P. H., and HUNTER, M. Low sodium chloride diets in hypertension — Effects on blood pressure J. Amer med. Ass., 140: 458, 1949
51 SCHWARTZ, W B., and MERLIS, J. K. Nitrogen balance studies on the Kempner rice diet. J. clin Invest, 27: 406, 1948.
52 SELYE, F. L. Biochemical changes in hypertension Canad med. Ass. J, 57: 325, 1947
53 SMIRK, F. H., and ALSTAD, K S. Treatment of arterial hypertension by penta- and hexamethonium salts. Brit med. J, 1: 1217, 1951.
54 STARKE, H. Effect of the rice diet on the serum cholesterol fractions of 154 patients with hypertensive vascular disease Amer. J Med., 9: 494, 1950
55 VERNEY, E B. and WINTON, F. R The action of caffeine on the isolated kidney of the dog. J. Physiol. (Lond), 69 153, 1930.
56 VOLHARD, F. Die Behandlung der Sklerosen Handbuch der inneren Medizin. Julius Springer, Berlin, 6: pt II, p 1758
57 WATKIN, D M, FROEB, H. F., HATCH, F T, and GUTMAN, A B. Effects of diet in essential hypertension. I Baseline study Amer J Med, 9 428, 1950
58 WESTON, R. E, HELLMAN, L, ESCHER, D. J. W, EDELMAN, I S, GROSSMAN, J., and LEITER, L. Studies on the influence of the low sodium cardiac diet and the Kempner regimen on renal hemodynamics and electrolyte excretion in hypertensive subjects J clin. Invest, 29: 639, 1950.

CHAPTER XVI

# HYPOTENSIVE DRUGS, MOSTLY OF ACADEMIC INTEREST

Although several of the drugs referred to in this Chapter are still used in combination with other drugs, they are mostly either insufficiently effective in non-toxic doses or when used as sole hypotensive agents. These drugs are not without interest, however, for better hypotensive agents than any we have at present may be found among their chemical relatives.

Physicians contemplating the use of veratrum alkaloids, hydralazine or dibenzylene in combination with Rauwolfia alkaloids or ganglion blocking agents may find it preferable to read a brief account of the action of certain combinations of drugs (see Chapter XX) before turning to the more detailed accounts given in this Chapter.

## VERATRUM ALKALOIDS

The use of veratrum preparations has never been entirely abandoned since the paper by Osgood (1835) who referred to its use for a variety of medical disorders and gave a dramatic account of his personal experiences with the drug.

The alkaloids for the most part are powerful hypotensive and bradycardic agents They suffer the disadvantage that the effective hypotensive dose is close to the emetic dose. Many pure alkaloids are now available in addition to several preparations of mixed veratrum alkaloids Clinical trials and animal experiments have been conducted with the aim of effecting a wider separation between the desired hypotensive action and the toxic effects — mainly nausea and vomiting.

From what follows it will be seen that pure derivatives, as well as various alkaloidal mixtures, activate a number of basic physiological mechanisms in a way which has made analysis of their action most complex.

The veratrum alkaloids are derived from liliaceous plants, notably *Veratrum album*, *Veratrum viride*, and *Schoenocaulon officinale*. These plants also contain amorphous material which is pharmacologically active but of uncertain composition, offering further scope for study. Many active substances have now been identified[139], and it is found that the different plant sources contain active principles in different

proportions; even in the same plant they vary with the conditions of growth.

While there are many similarities in the actions of various alkaloidal mixtures and pure veratrum alkaloids, the doses required to produce such effects vary considerably. Maison, Gotz and Stutzman (1951) report that the relative hypotensive potencies of fifteen substances derived from veratrum plants and compared with a standard reference Veriloid powder (taken as 1) were: germitrine 11, neogermitrine 8.7, germerine 5.3, protoveratrine 4.7, germidine 2.4, veratridine 0.5, veratrine 0.3, cevadine 0.10, veratramine 0.03. They state that germine, rubijervine, jervine, isorubijervine and pseudojervine were weak in action and that it was impossible to eliminate the possibility that such action as was present was due to contamination with more active substances. In a study of hypotensive activity, the dose-response curves of protoveratrine and of veratridine were parallel, which suggested that a similar type of hypotensive mechanism was involved in each case.

*Biological assay.* — Assays of the activity of several veratrum derivatives have been made by observing their capacities to arrest the heart in *Daphnia magna*, a species of "water flea". This action is the basis of the Craw unit of activity. Assays have been made also using frogs, mice, rats, pigeons, guinea-pigs, rabbits and dogs; and comparative studies have been made of the response in man. In so far as the desired property is blood pressure reduction, there is much to be said for assays which make use of the hypotensive action. A standard alkaloidal extract of *Veratrum viride* — namely Veriloid — has been shown to have a reproducible composition [234]. This extract has been used as a standard reference powder with which to compare the hypotensive activity in dogs of several veratrum derivatives [155] There is much to be said, however, for using as standard a pure substance such as protoveratrine or neogermitrine as these are now more readily available.

It has been shown (Swiss, 1952) that emesis in dogs runs closely parallel to hypotensive activity and that there is practically no difference in the relationship of the two effects as one passes from one alkaloidal substance to another. The emetic dose in the pigeon has been used for assay by Christensen and MacLean (1936). Maison and Stutzman (1951) consider that studies of the $LD_{50}$ are unsatisfactory for assay as lethal toxicity does not necessarily run parallel with hypotensive activity. Freis, Stanton and Moister (1950) and Doyle and Smirk (1953) rely on direct studies of the hypotensive activity in man following intravenous injection.

## Experimental Pharmacology

Fortunately it happens that within the therapeutic range, the manifest actions of the veratrum derivatives which are employed clinically are very similar to one another, the principal difference being

in dosage. Not only is the hypotensive effect similar, but also the relationship of the principal side effects to the clinically desired action does not vary much.

## Circulatory Effects of Veratrum Alkaloids

*Effect on the blood pressure.* — Much work has been carried out on the causation of the blood pressure fall following the administration of veratrum alkaloids. Stutzman and Maison (1950) and Stutzman, Simon and Maison (1[illegible] experiments with Veriloid, a mixed alkaloidal preparatio[illegible] bilateral vagotomy. [illegible] veratrum alkaloids, bilateral vagotomy abolished the bradycardia, it made no important chan[illegible] also made a preparation in w[illegible], the vagi were left intact but [illegible] the head was perfused with Veriloid there was a profound blood pressure fall but no change in the heart rate. When Veriloid was given into the general circulation, the head being excluded, there was bradycardia and hypotension, but after the administration of atropine both the bradycardia and the hypotension were abolished. The authors concluded that the bradycardia after Veriloid is dependent on a reflex (the von Bezold reflex) but vasodilatation is due to decrease of the activity of vasomotor centres in the brain. Stutzman, Simon and Maison (1951) showed that germitrine, protoveratrine, germidine, germerine, vera[illegible] and veratramine resembled the Veriloid mixed alkaloids in

[illegible]

by Taylor and Page (1951) led to marked falls of blood pressure when veratrum alkaloids were injected into the head circulation.

These conclusions differ from those of Krayer and Acheson (1946) who considered that the evidence then available favoured the view that the Bezold reflex was the main factor in determining hypotension. This reflex was described by von Bezold and Hirt (1867), who attributed the fall in blood pressure and the bradycardia after veratrum alkaloids to reflexes arising from the heart itself, and due to the stimulation by veratrum of nerve endings in the heart muscle; the afferent pathway

[illegible]

which carry bursts of electrical activity in phase with the heart beat and which can be caused to discharge continuously after veratrine. Jarish and Richter (1939) (using veratrine), and Dawes (1947) (using protoveratrine, veratridine and cevadine) also thought that the fall of blood pressure arose mainly from a cardiac and to a much lesser extent from a pulmonary reflex, the afferent pathway being vagal. A most

convincing experiment in favour of the Bezold reflex causing hypotension through a vagal action is the experiment of Jarish and Richter (1939) in which they demonstrated that the blood pressure fall after veratrum alkaloids was reduced by blockading the vagi by cold and hypotensive activity developed when vagal conduction was restored by warming.

During the fall of blood pressure induced by veratrum alkaloids there is evidence of vascular dilatation in many regions of the body. This was demonstrated in the liver by Jarish and Richter (1939), in the intestines and kidneys by Cramer (1915); the authors' experiments being made on cats. An increase of blood flow in the hind limb of the dog was noted after protoveratrine (Krayer, Moe and Mendez, 1944) and after veratridine (Moe, Bassett and Krayer, 1944).

It was shown by Stutzman, Simon and Maison (1951) that the carotid sinus was not necessary for the hypotensive action. The decrease in the carotid sinus pressure reflex under the action of veratrum derivatives which has been described by Richardson et al. (1951) and by Rubin and Burke (1952) may be influenced by alterations in the blood pressure level (Prochnik et al., 1950) or be due to central vasomotor inhibition by veratrum. Changes in carotid sinus activity do not seem to explain the fall in blood pressure. An interesting experiment was performed by Waud et al. (1955), who administered veratrum alkaloids to dogs, with the heart and lungs replaced by a pump and oxygenator. The preparation exhibited no blood pressure fall when the veratrum alkaloids were given. This is evidence for a cardiac action.

A direct action on isolated blood vessels was reported by Willson and Smith (1943) in perfusion experiments, using veratrone, an injectable mixed alkaloid preparation. The concentration of veratrum alkaloid used, however, was high. The cross-circulation experiments of Krayer, Moe and Mendez (1944) and of Moe, Bassett and Krayer (1944) indicate that with veratrine, veratridine and protoveratrine at least, the direct effect on blood vessels of doses comparable with those used therapeutically is unimportant when compared with the neurogenic effects.

It was shown by Papacostas, Mountain, Maison and Bauer (1952) that anaesthesia with pentobarbital lessens the hypotensive action of Veriloid in dogs.

To sum up: the experiments which have been reported in the literature involve a large number of active substances and a variety of animals and modes of administration. The general impression is that vagal slowing of the heart may reduce the blood pressure, particularly when there is a rapid administration of veratrum alkaloids. This type of hypotensive activity is to be found with most of the active alkaloids and alkaloidal mixtures and is abolished by atropine; but, neither atropine nor bilateral cervical vagal section prevents the main fall of

blood pressure, particularly that which occurs with more gradual administration of the substances. The consensus of opinion *is that an* important, possibly the main, hypotensive effect is an *action of the* veratrum alkaloids, pure or mixed, on brain centres leading to peripheral vasodilatation. It is generally agreed that, in doses which may be administered to patients, direct action on blood vessels is absent or

[illegible]

the slowing of the heart rate following the administration of veratrum alkaloids is of vagal origin. The slowing action may be prevented by atropine or by section of both cervical vagi. The evidence previously referred to strongly suggests that the bradycardia is due to a von Bezold reflex, which takes its origin from the stimulation of nerve endings in the heart by veratrum alkaloids.

The isolated perfused heart, it is true, is influenced to some extent by veratrum alkaloids, there being a strengthening of contraction mainly when the heart's action is flagging. This positive inotropism may be demonstrated also in the heart-lung preparation. Such observations have been made by Hedbom (1898), Kuliabko (1905), Krayer and Mendez (1942) and by Stearns and Maison (1950). Some of the above authors have reported a direct slowing of the heart, others an increase in the heart rate, the difference in effect apparently depending on the alkaloid and the animal used for the experiment. It is, however, generally agreed now that the direct effects on the heart are subsidiary to the vagal bradycardia observed in the whole animal.

In the isolated heart, disturbances of rhythm may be induced by veratrum which may occur also in the whole animal (Stearns and Maison, 1950), such as prolongation of the a-v interval, heart block and premature systoles. These may sometimes be abolished by atropine.

Mosey, Maison and Stutzman (1951) showed that, in dogs, disturbances of rhythm produced by excessive doses of digitoxin and ouabain were exaggerated by Veriloid; the animal showed additional slowing of the heart rate On the other hand, the combination of quinidine hydrochloride and Veriloid was not productive of arrhythmias and, as might be expected from the vagal blocking action of quinidine, the bradycardia from Veriloid was diminished by quinidine.

### Other Pharmacological Effects

*Effect on respiration.* — It has long been realized that many veratrum derivatives decrease pulmonary ventilation and *in large doses* may give rise to respiratory arrest. As far back as 1867 the experiments of von Bezold and Hirt suggested that the action was a *reflex* similar to that which slows the pulse. The doses of the individual alkaloids required to induce respiratory depression vary considerably, as indeed

convincing experiment in favour of the Bezold reflex causing hypotension through a vagal action is the experiment of Jarish and Richter (1939) in which they demonstrated that the blood pressure fall after veratrum alkaloids was reduced by blockading the vagi by cold and hypotensive activity developed when vagal conduction was restored by warming.

During the fall of blood pressure induced by veratrum alkaloids there is evidence of vascular dilatation in many regions of the body. This was demonstrated in the liver by Jarish and Richter (1939), in the intestines and kidneys by Cramer (1915); the authors' experiments being made on cats. An increase of blood flow in the hind limb of the dog was noted after protoveratrine (Krayer, Moe and Mendez, 1944) and after veratridine (Moe, Bassett and Krayer, 1944).

It was shown by Stutzman, Simon and Maison (1951) that the carotid sinus was not necessary for the hypotensive action. The decrease in the carotid sinus pressure reflex under the action of veratrum derivatives which has been described by Richardson et al. (1951) and by Rubin and Burke (1952) may be influenced by alterations in the blood pressure level (Prochnik et al., 1950) or be due to central vasomotor inhibition by veratrum. Changes in carotid sinus activity do not seem to explain the fall in blood pressure. An interesting experiment was performed by Waud et al. (1955), who administered veratrum alkaloids to dogs, with the heart and lungs replaced by a pump and oxygenator. The preparation exhibited no blood pressure fall when the veratrum alkaloids were given. This is evidence for a cardiac action.

A direct action on isolated blood vessels was reported by Willson and Smith (1943) in perfusion experiments, using veratrone, an injectable mixed alkaloid preparation. The concentration of veratrum alkaloid used, however, was high. The cross-circulation experiments of Krayer, Moe and Mendez (1944) and of Moe, Bassett and Krayer (1944) indicate that with veratrine, veratridine and protoveratrine at least, the direct effect on blood vessels of doses comparable with those used therapeutically is unimportant when compared with the neurogenic effects.

It was shown by Papacostas, Mountain, Maison and Bauer (1952) that anaesthesia with pentobarbital lessens the hypotensive action of Veriloid in dogs.

To sum up: the experiments which have been reported in the literature involve a large number of active substances and a variety of animals and modes of administration. The general impression is that vagal slowing of the heart may reduce the blood pressure, particularly when there is a rapid administration of veratrum alkaloids. This type of hypotensive activity is to be found with most of the active alkaloids and alkaloidal mixtures and is abolished by atropine; but, neither atropine nor bilateral cervical vagal section prevents the main fall of

are very *closely* associated *in man*. This important observation made with so many different veratrum derivatives shows that it may be [illegible] any additional member of this group of substances [illegible]

[illegible]

emesis in dogs. Animals having emesis also had repeated [illegible] which occurred almost simultaneously. In some instances the dogs collapsed and had clonic movements.

*Swiss studied* the effect of scopolamine, atropine, ephedrine, tetraethylammonium chloride, dramamine and banthine on the emesis. Banthine may have had a slight beneficial action but otherwise none of the other substances led to *amelioration of the symptom*.

*Effect on the intestines.* — The demonstration in perfusion experiments of a direct effect on the muscle of blood vessels by very large doses of veratrum alkaloids (Willson and Smith, 1943) and the contraction of bronchioles even in the presence of atropine (Mosey and Kaplan, 1952) may stand in relation to the demonstration by Gourzis and Bauer (1951) that many veratrum derivatives: germerine, protoveratrine, germidine, veratridine and cevadine as well as the standard Veriloid reference powder, give rise to an increase in the tone of rabbit intestine when placed in an organ bath. This action is not inhibited by doses of atropine which are ordinarily used to inhibit parasympathetic effects but is somewhat diminished by very large doses There is a strong suggestion that this action is directly upon the musculature of the intestines When, however, Veriloid is administered intravenously in trained unanaesthetized dogs, no intestinal stimulation which could be attributed to the Veriloid was seen prior to emesis. It would appear that this direct action upon intestines, though definite enough in an organ bath, is not likely to be encountered in the doses ordinarily employed therapeutically Swiss (1952), however, encountered defecation as a sign of toxicity

*Effect on striped muscle.* — The mixed alkaloid preparation Veratrine has long been known to cause prolongation of the contraction of striped muscle The literature has been reviewed by Krayer and Acheson (1946) It has become evident (Bacq, 1939 a, b) that most, if not all, of the actions of Veratrine on the muscle fibre, and possibly of other actions, are explained by *increase of the* response to potassium. Goutier (1949) has now shown that protoveratrine, veratridine, cevadine, jervine, rubijervine, cevine and germine sensitize isolated amphibian striped muscle to potassium ions and lead to prolongation of contraction. He states that this action roughly parallels their general toxicity.

## Clinical Studies with Veratrum Alkaloids

The veratrum derivatives include some of the most powerful hypotensive agents known. In most respects clinical experience with

they do for most of their well-known effects. It appears, however, that the effects on respiration are commonly in proportion to the effects on blood pressure. If the doses of the various veratrum deriva- [illegible]

Thus, Mosey and Kaplan (1952) studied veratridine, germidine, germitrine, neogermitrine, germerine, protoveratrine, alkaloid G., alkaloid V.B., as well as a mixture of alkaloids, Veriloid. A dose approximating to the clinically desired dose in dogs has only a transitory effect in depressing respiration. When three times this standard hypotensive dose was administered, most of these veratrum alkaloids depressed pulmonary ventilation by 40 to 60 per cent. Observations by Mosey and Kaplan (1952) suggest that there are two components which lead to the decrease in ventilation. First, a depression of the respiratory centre and, second, bronchoconstriction which is either due to a direct action upon the bronchial smooth muscle or to some reflexes which are not vagal and not cholinergic. It is not yet clear whether a von Bezold type of reflex has a contributory action. Three alkaloids, however, cevadine, veratramine and veratrine, produced respiratory stimulation.

*Emetic action.* — Emesis, the most conspicuous of the toxic effects of veratrum derivatives, was reported by Osgood (1835). This effect has been studied in detail recently by Swiss (1952) who introduced Veriloid into the stomach after pyloric ligature. He found that the Veriloid was not significantly absorbed from the stomach and that stomach irritation was but a minor factor in the production of vomiting. He also found that denervation of the gastro-intestinal tract did not prevent emesis after the administration of Veriloid, and eventually concluded that vomiting is due to the stimulation of the vomiting centre in the medulla. This view is in agreement with the conclusions of Christensen and McLean (1936) and of Marsh, Herring and Howard (1951). Borison and Fairbanks (1952), however, did not accept this site of action, as they found that interruption of the vagus nerve above the nodose ganglion prevented veratrum emesis in the cat.

Swiss (1952) made observation with 22 different preparations; some were pure alkaloids, others were alkaloidal mixtures. For each pure substance and mixture he discovered in a large number of dogs (1) the dose in mg./kg. of the drug necessary to cause emesis in 50 per cent of the animals tested and (2) the hypotensive dose sufficient to produce an average fall of the mean arterial blood pressure of 30 per cent. Among the various substances tested there was a very high correlation between the emetic dose and the hypotensive dose, there being a straight line relationship between the log. of the standard hypotensive dose and the log. of the emetic dose (E.D. 50). These results are consistent with the finding that the hypotensive and the emetic doses

$LD_{50}$ for an oral dose. A degree of destruction of oral doses seems likely.

Absorption of a veratrum derivative is delayed when oral administration follows a meal and a dose which induces hypotension and emesis when administered before a meal may have neither action if given after. Smirk and Chapman (1952) and Doyle and Smirk (1953) thought the effects of oral administration were more regular, there being fewer unexpected toxic episodes, if the veratrum preparations they used were given before meals, but the doses had to be smaller. Even so, there were sometimes substantial differences in action from day to day, as is shown in the following table:

TABLE XVI 1. *Variations in the Magnitude of the Blood Pressure Fall After Oral Doses of Veratrum Alkaloids*

(Smirk, F. H., and Chapman, O. W. Amer. Heart J., 43: 586, 1952)

| Case No | Date | Dose* | Resting B P Before Drug | Minimum B P After Drug | Maximum Fall |
|---|---|---|---|---|---|
| 163 | 2/12/50 | 2½:1¼ V | 206/118 | 150/80 | 56/28 |
| | 9/12/50 | 2½:1¼ V | 180/110 | 110/60 | 70/56 |
| 82 | 23/12/50 | 2:1 V | 190/120 | 140/106 | 50/14 |
| | 20/ 1/51 | 2.1 V | 180/120 | 90/50 | 90/70 |
| 20 | 2/12/50 | 2·2 1 A | 220/125 | 150/85 | 70/40 |
| | 9/12/50 | 2·2 1 A | 230/130 | 220/120 | 10/10 |
| 77 | 17/12/50 | 3½ 1½ A | 170/110 | 160/110 | 10/0 |
| | 15/ 3/51 | 3·1 A | 175/112 | 114/60 | 61/52 |
| 154 | 19/ 1/51 | 2 2 A | 252/132 | 172/108 | 80/24 |
| | 27/ 1/51 | 2:2 A | 254/132 | 136/94 | 118/38 |

* The letter "A" refers to Anatensol tablets (0 5 mg ). The letter "V" refers to Vertavis tablets (10 Craw units)

The figures refer to the number of tablets given; where two or more figures are given, the tablets have been given at hourly intervals in the number indicated by the figures

It is, however, of very great interest that, in man, the gap between the hypotensive dose and the emetic dose is much wider when at least certain veratrum alkaloids are given parenterally than when they are given orally. These results are not entirely explained by the more exact control over the absorbed dose which attends parenteral administration.

pure alkaloid and mixed alkaloid preparations are consistent with the results of animal experiments. It is generally agreed [19, 61, 71, 121, 133, 228, 265], that when mixtures of the veratrum alkaloids are given by mouth the onset of significant hypotensive activity begins with a dose which is only a little less than the toxic dose. The principal toxic effect is vomiting. Before describing the effects in detail reference will be made to some of the preparations used clinically. The toxicity of crude mixed alkaloid preparations led to the use clinically of more refined mixtures and of pure derivatives. Unfortunately, none of the pure alkaloids at present available seem to offer a distinct advantage over mixed alkaloidal preparations [61, 265].

Doyle and Smirk (1953) found that, except in acute experiments, oral protoveratrine and neogermitrine did not seem much, if any, better than oral Anatensol, Vertavis or Veriloid. During the first month of treatment protoveratrine appeared to have a slight advantage. They noted that patients reacted to most veratrum preparations (pure substances or mixtures) in the same way. The failures failed with all, and the successful managed almost equally well on a variety of preparations. Hoobler, Corley, Kabza and Loyke (1952) reported satisfactory results in the treatment of hypertension with oral protoveratrine. They considered protoveratrine superior to Veriloid; but with protoveratrine, as with other veratrum derivatives, meticulous control of dosage was required to avoid toxicity. While there may be little difference between one substance and another as judged by a survey of the responses of patients or of animals, yet there may be an important difference in the gap between the emetic dose and the hypotensive dose in one patient as compared with another. Some patients are much more tolerant than the average of effective hypotensive doses.

## Oral and Parenteral Dosage

Animal experiments indicate that gastric irritation is unimportant in the causation of emesis In man doses of veratrum derivatives sufficient to induce either hypotension or vomiting have to be larger when given by mouth than when injected — probably because of slower or incomplete absorption from the intestines.

For example, Doyle and Smirk (1953) described a patient who had approximately equal blood pressure falls (average 70/50) from 0.27 mg. of neogermitrine given intravenously over 22 minutes as from 1.3 mg. by mouth. In six tests effective falls of blood pressure were induced by doses of 0.19 to 0.3 mg. of protoveratrine given intravenously with nausea in one patient. With oral protoveratrine the maximal sub-toxic dose ranged from 0.5 to 1.25 mg. and the minimum toxic dose was 0.62 to 2 mg. In animals Haas (1938) found with protoveratrine and germerine that the $LD_{50}$ for a subcutaneous dose was about ⅛ of the

hypotensive and the toxic dose narrowed with repeated administration.
The relation of the hypotensive to toxic effects of the intravenous and oral routes of administration are set out in Tables XVI 2 and XVI 3 for neogermitrine and protoveratrine.

Stearns and Ellis (1952) were able to give Veriloid intravenously in 36 tests on 25 patients with significant falls of blood pressure. There was vomiting in 8 tests and nausea in an additional 5. They refer to

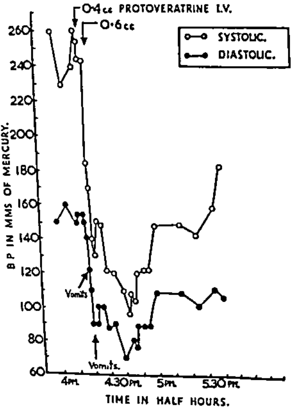



Fig XVI 2

Effect of intravenous protoveratrine (1 c c. = 0 2 mg.). (Smirk, F. H., and Chapman, O W., Amer. Heart J., 43 : 586, 1952).

a fall of blood pressure by ng but could tolerate intra- ... Assali (1950) using veratrone in toxaemia of pregnancy and eclampsia found the intravenous route preferable for acute emergencies. On the other hand Shapiro and Ferris (1952), who gave veratrone intravenously, encountered nausea and vomiting in one-third of their patients. Goldman and Frierson

Meilman and Krayer (1952) for example had no instance of vomiting in a series of 284 intravenous injections of protoveratrine. Nausea or substernal discomfort occurred 18 times. The same authors found that protoveratrine could usually be given intramuscularly without the occurrence of side effects, but in five out of fifteen patients oral protoveratrine caused no blood pressure fall in doses which caused nausea or extreme bradycardia. Doyle and Smirk (1953) found that very large

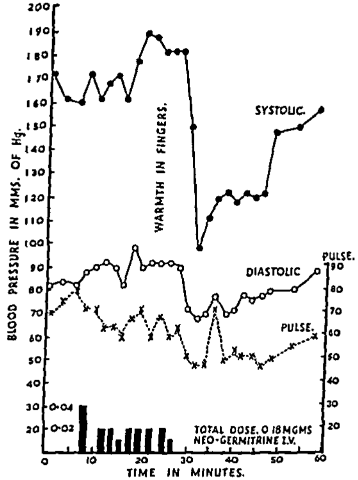



Fig. XVI 1

Example of abrupt fall of blood pressure beginning at a critical dose in the course of slow injection of neogermitrine. (Doyle, A. E, and Smirk, F H., Brit. Heart J., 15 . 430. 1953)

falls of blood pressure could be produced in almost all instances without vomiting by intravenous or by intramuscular injection of neogermitrine or protoveratrine. Much smaller blood pressure falls induced by oral administration of these substances were often attended by vomiting. Treatment by protoveratrine or neogermitrine, by intramuscular injections, was not usually of lasting value as the gap between the

(1953) gave Venloid intravenously and nausea and vomiting occurred in slightly more than half of their patients.

A comparison of effects on the blood pressure of the maximum subtoxic dose and the first dose to induce toxicity was made by Doyle and Smirk (1953) using protoveratrine and neogermitrine. It will be seen (Tables 2 and 3) that the difference between the hypotensive and the toxic dose is very small. It is evident that dosage with veratrum derivatives is highly critical (Figs. XVI 1 and XVI 2). First doses given to patients should be at the lower end of the scale and dosage increase should be by small increments. The alkaloidal mixtures used clinically should be of reproducible strength.

TABLE XVI 3. *Effect on Blood Pressure of Oral Administration of Protoveratrine*

(Doyle, A. E., and Smirk, F. H. Brit. Heart J., 15: 430, 1953)

| Case No | Maximal subtoxic dose (protoveratrine) (mg) | Blood pressure fall | Toxic dose (mg) | Blood pressure fall | Result of test |
|---|---|---|---|---|---|
| 191 | 1 0 | 0/0 | 1.25 | 54/38 | Failed |
| 203 | 0 5 | 0/0 | 0.75 | 70/40 | Failed |
| 33 | 1.0 | 30/20 | 1.25 | 138/100 | Failed |
| 169 | 1 0 | 70/22 | Not reached | — | Success |
| 162 | 1 25 | 80/56 | Not reached | — | Success |
| 157 | 1.0 | 64/30 | Not reached | — | Success |
| 16 | 1.25 | 30/14 | 1.5 | 64/38 | Failed |
| 61 | 0 5 | 0/0 | 0.625 | 88/60 | Failed |
| 204 | 1.75 | 72/44 | Not reached | — | Success |
| 221 | 0 625 | 34/22 | 0.75 | 42/38 | Failed |
| 178 | 1.0 | 30/14 | 1.25 | 60/24 | Failed |
| 193 | 0 5 | 0/0 | 0 75 | 72/60 | Failed |
| 202 | 0 75 | 38/12 | 0.875 | 50/36 | Failed |
| 161 | 1.0 | 30/18 | 1.25 | 50/38 | Failed |
| 207 | 1.25 | 0/0 | 1.5 | 98/58 | Failed |
| 159 | 1 5 | 130/62 | 2 0 | 150/70 | Success |
| 152 | 1.25 | 76/39 | Not reached | — | Success |

## Drug Toleration

There has been doubt as to whether the body acquires a toleration for veratrum alkaloids. It is generally agreed that, if there is such a tolerance, it is small if a comparison is made with the rate of development and extent to which toleration develops after the administration

TABLE XVI 2 *Effect on Blood Pressure of Oral Administration of Neogermitrine*

(Doyle, A. E., and Smirk, F. H. Brit. Heart J., 15: 439, 1953)

| Case No. | Maximal subtoxic dose (neogermitrine) (mg.) | Blood pressure fall | Toxic dose (mg.) | Blood pressure fall | Result of test |
|---|---|---|---|---|---|
| 191 | 0.85 | 10/6 | 0.9 | 73/34 | Failed |
| 61 | 0.5 | 32/12 | 0.55 | 48/16 | Failed |
| 258 | 0.7 | 52/44 | 0.8 | 74/32 | Success |
| 203 | 0.75 | 90/20 | 0.75 | 100/46 | Failed |
| 162 | 1.0 | 84/46 | 1.1 | 130/56 | Success |
| 202 | 0.55 | 56/32 | Not reached | — | Success |
| 161 | 0.55 | 0/0 | 0.6 | 20/5 | Failed |
| 103 | 0.7 | 40/28 | 0.8 | 82/68 | Failed |
| 268 | 0.6 | 42/16 | 0.65 | 84/66 | Failed |
| 221 | 0.4 | 21/12 | 0.5 | 44/32 | Failed |
| 40 | 0.5 | 16/6 | 0 6 | 78/44 | Failed |
| 171 | 0.6 | 18/6 | 0.7 | 84/36 | Failed |
| 165 | 0.8 | 74/32 | Not reached | — | Success |
| 137 | 0.5 | 26/8 | 0.6 | 64/28 | Failed |
| 261 | 0.5 | 32/12 | 0.6 | 52/34 | Failed |
| 172 | 0.6 | 36/20 | 0.7 | 68/46 | Failed |
| 152 | 0.8 | 64/48 | Not reached | — | Success |
| 182 | 0.6 | 38/22 | 0.7 | 84/44 | Failed |
| 193 | 0.9 | 0/0 | 1.0 | 40/32 | Failed |
| 16 | 0.9 | 28/16 | 0.95 | 16/8 | Failed |
| 204 | 1.3 | 84/44 | 1.4 | 86/44 | Success |
| 178 | 0.95 | 30/10 | 1.0 | 60/22 | Failed |
| 321 | 0.6 | 18/6 | 0.7 | 60/14 | Failed |
| 223 | 0.55 | 22/24 | 0.6 | 132/54 | Failed |
| 167 | 0.7 | 64/42 | Not reached | — | Success |
| 206 | 0.8 | 18/10 | 0.85 | 72/30 | Failed |
| 194 | 0.9 | 56/48 | 1.0 | 148/64 | Failed |
| 183 | 0.6 | 32/14 | 0.7 | 86/64 | Failed |
| 298 | 0.9 | 28/18 | 1.0 | 20/6 | Failed |
| 300 | 0.5 | 42/32 | 0 6 | 80/52 | Success |
| 305 | 0.9 | 28/18 | 1.0 | 128/82 | Failed |
| 318 | 0.6 | 20/12 | 0.7 | 82/40 | Failed |
| 320 | 0.6 | 8/2 | 0.7 | 70/24 | Failed |
| 325 | 0.5 | 46/21 | Not reached | — | Success |

have been made by Freis et al. (1949a) and by Wilkins, Freis and Stanton (1949). In conformity with the absence of notable falls in cardiac output are the reports that, although bradycardia in man may be abolished by atropine, *the fall in blood pressure is maintained*. After atro[illegible] Ferris (1952) found only an insignificant decr[illegible]
Corey [illegible]
pressure falls induced by protoveratrine. On the other hand, [illegible] and Krayer (1952) *found the blood pressures* were somewhat lower after protoveratrine when bradycardia was present. Ruskin and Rider (1950), using Vertavis, found that 1·2 mg. of atropine partly reversed the hypotensive effect but did not abolish circulatory collapse.

Some writers have stated that a fall in blood pressure after veratrum alkaloids is not ordinarily accompanied by postural hypotension (Wilkins, Freis and Stanton, 1949) and others have reported postural hypotension (Shapiro and Ferris, 1952) using intravenous veratrone. Smirk and Chapman (1952) following oral administration of Vertavis or Anatensol observed comparatively little postural hypotension, except after excessive lowering of the blood pressure. They noted postural hypotension when large blood pressure falls followed intravenous administration of protoveratrine, as did Doyle and Smirk (1953) after intravenous protoveratrine or intravenous neogermitrine (Fig. XVI 3). A review of the various writings suggests that great blood pressure falls, especially when rapidly induced, are accompanied by postural hypotension, though not of the magnitude commonly seen after injections of hexamethonium bromide. Blood pressure falls more slowly induced and of a less extreme degree are not associated with much postural change

The overswing of the blood pressure following the Valsalva manoeuvre is said to occur in a normal way after veratrum alkaloids (Wilkins, Freis and Stanton, 1949), but it is possible that, like postural hypotension, the response to the Valsalva manoeuvre may depend upon the dose administered Observations on this point seem to be unavailable at present

An interesting reaction to veratrum hypotension is cited by Mills and Moyer (1952) a patient with phaeochromocytoma (proved at surgery) responded to hypotension induced by intravenous infusion of Veriloid by a considerable rise in pressure followed with rapid heart beat and sweating We have observed a similar incident after hexamethonium bromide in a surgically proved case.

Assali et al (1950) state that the administration of TEAC at the time of maximum veratrum effect opposes many of the manifestations of veratrum Perhaps this may be taken as evidence that veratrum alkaloids act through the intermediation of autonomic nerves and therefore the action is diminished or prevented by ganglionic blockade.

of hexamethonium bromide. Gropper, Surtshin and Hedrick (1951) report no development of drug toleration with continued administration of Veriloid. Barrow and Sikes (1951) thought a degree of tolerance to Anatensol was exhibited in some patients. We have observed this with mixed and pure alkaloids. What has been more conspicuous, however, has been the narrowing of the margin between the therapeutic and the toxic doses, such that when the dose is adjusted to avoid side effects the hypotensive action is lost or much diminished.

## Hypotensive Action

Clinical studies of the hypotension induced by veratrum derivatives are consistent with the results of animal experiments. The falls of blood pressure induced by the veratrum derivatives at suitable dosage levels

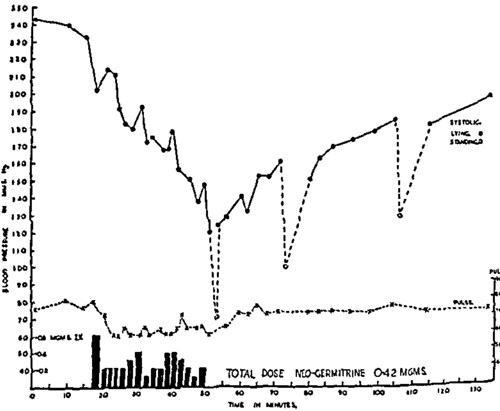



Fig XVI 3

Prolonged blood pressure fall persisting after intravenous neogermitrine, with demonstration of postural hypotension. (Doyle, A E, and Smirk, F. H. Brit Heart J, 15 : 439, 1953).

are of impressive magnitude, yet, according to most observers, the cardiac output is not much altered. This suggests dilatation of the peripheral blood vessels as the cause of the blood pressure fall.

Studies of the effects of veratrum derivatives on the cardiac output

Goldman and Frierson (1953) made observations with Veriloid and also noted profound initial oliguria and reduced glomerular filtration rate with little change in the renal plasma flow.

## Splanchnic Circulation

Measurement of the hepatic portal flow using the bromsulphonphthalein method[35] shows a brief reduction in blood flow followed by a rise above the original level[267]. This observation was confirmed by Freis et al. (1949c).

## Limb Circulation

[illegible]

the blood pressure was still low[76, 78, 123].

## Effect on Heart Rhythm

Effective hypotensive doses of all veratrum derivatives cause sinus bradycardia with the heart rates usually below 60, often below 50 (Fig. XVI 1). Heart rate [illegible] than in the standing pos[illegible] hypotension (Smirk and [illegible] the minimum blood pressure might continue [illegible] earlier *In some patients hypotension and bradycardia were so consistently associated that pulse slowing enabled the patient to say when blood pressure falls had occurred*

It is generally accepted that in man, as in animals, the bradycardia may be abolished by blocking the vagus nerve terminals with atropine and it seems highly probable that the heart slowing is caused by the von Bezold reflex Vagal blockade, however, does not prevent such side effects as emesis In some patients at least, vagal block by atropine lessens the extent of the blood pressure fall while in others the influence of atropine on the blood pressure fall is negligible.

Cardiac arrhythmias occasionally develop during the action of mixed veratrum alkaloids and similar arrhythmias occur with protoveratrine In addition to bradycardia there may be prolongation of the A-V interval, partial or even complete heart block[64, 124, 229], premature ventricular systoles[64, 160, 265] and, on occasion, ventricular paroxysmal tachycardia. We encountered a fit patient who developed auricular fibrillation during the start of veratrum treatment. Quinidine restored normal rhythm Nodal rhythm has been reported by several authors[64, 149, 159, 229]

In 168 trials with intravenous protoveratrine Meilman and Krayer

## Cerebral Circulation

The clinical impression is that the brain does not suffer as the result of blood pressure reduction by veratrum alkaloids; except at distinctly hypotensive levels. There appears to be a decrease in the cerebral vascular resistance [49, 50, 162] and the cerebral blood flow is normal [49] or slightly diminished [50, 162]. The cerebral arteriovenous difference and cerebral oxygen consumption are not greatly altered.

## Retinal Circulation

Willson and Smith (1943) have reported striking dilatation in the retinal vessels following veratrum alkaloids in a patient with eclampsia. Similar changes of lesser degree have been observed by others (Freis and Stanton, 1948) at the time of a strong veratrum action.

## Renal Circulation and Excretion

In man there is evidence of decrease in renal resistance enabling an approximately normal blood flow to be maintained despite the blood pressure fall. The concentration of solid constituents in the urine increases during at least the initial phases of veratrum hypotension, but the urine volume is decreased. After some hours the urine flow begins to return towards the original level. Certainly under clinical conditions there is no important change in renal excretion in patients whose renal function tests were satisfactory before the veratrum was given.

Wilkins, Freis and Stanton (1949), using Vertavis, found that the blood was cleared as efficiently as before the Vertavis despite the smaller volume of concentrated urine. Hoobler and Corley (1950) found the urine volume decreased almost to half after protoveratrine. The renal plasma flow was maintained despite the fall of blood pressure, indicating a decrease in resistance of the renal blood vessels. Meilman (1953) also studied the effect of protoveratrine. During the initial phases of its action the effective renal plasma flow was usually diminished (average —8 per cent) and the glomerular filtration rate usually fell to a striking extent (average —22 per cent), and the characteristic oliguria was present. If the fall of blood pressure was maintained by continued administration of these substances there was, however, no impairment of renal excretion and the oliguria passed off. Meilman used the inulin clearance for the determination of glomerular filtration rate and estimated the effective renal plasma flow by the clearance of sodium para-amino-hippurate. Renal resistance was calculated as

$$\frac{\text{mean blood pressure (mm Hg)}}{\text{effective renal blood flow (cc. per min.)}}$$

Coronary insufficiency is not likely to be the usual explanation of the T wave changes induced by veratrum alkaloids. It is highly

pressure in patients with organic ... attacks may occur in such patients if the blood pressure is reduced below a critical level by any means. We have observed this on a number of occasions in hexamethonium and in veratrum hypotension. Angina after veratrum is not as easy to relieve as after hexamethonium because, ordinarily, the blood pressure after veratrum does not rise again in the lying posture.

### Effect on Respiration

There is little mention in th ... following the administration ... (1952) refer to the unpublished observations of ... occasionally noted transient, but never gross, respiratory depression in the course of 200 intravenous administrations of Verloid.

## Toxic or Side Effects of Veratrum Alkaloids

The usual symptoms of toxicity after oral doses of Vertavis, Anatensol or Verloid are nausea, salivation, sweating, pallor, and general misery, often followed by vomiting, sometimes violent and repeated. Some patients vomited without having much malaise; others were ill and unable to stand, though they recovered usually within an hour. Diarrhoea has occurred. Tingling about the fingers, lips, tongue, and feet were common but not disturbing. A frightening sensation of constriction in the throat and upper chest was common and sometimes associated with inability to swallow Those who had this symptom often would not persist with the drug. In some instances a milder ... trosternal and ... . The profound ... of the chest. Blurring of the vision is complained of occasionally. These symptoms are encountered in almost all patients during preliminary trials with oral doses if the aim is to reduce the blood pressure to near normal levels. With oral doses there may be no substantial fall of blood pressure (e g. less than 40/20) even when symptoms of toxicity are present. The blood pressure, however, sometimes falls rapidly with the onset of toxicity to a level of about 80/60 and sometimes, ... state develops at such levels ... be alarming. Many authors s... results from oral dosage either do not occur or are of rare occurrence. Though the symptoms of substantial toxicity are unpleasant, all our patients recovered within a few hours. When veratrum alkaloids are given

(1950) found that "first degree heart block occurred four times, nodal rhythm twelve times, ventricular extrasystoles twice, bigeminy twice and Wenckebach phenomenon twice in 10 patients of whom 4 were digitalized."

It has been noted several times that arrhythmias of the types referred to above have disappeared after atropine [64, 124].

## The Combination of Veratrum Alkaloids and Digitalis

Clinical reports confirm the need for caution in the simultaneous use of digitalis and veratrum alkaloids. As in animal experiments, bradycardia may be excessive when the two drugs are used together. Meilman and Krayer (1952) state that numerous premature systoles may follow the administration of protoveratrine to a digitalized patient. This, however, was not an invariable occurrence. Shapiro and Ferris (1952) reported that the effect of the combination on the heart rate could not be antagonized by atropine. Stearns and Ellis (1952) reported a death which might have been due to this combination of drugs; the patient developed a nodal rhythm, later a Stokes-Adams syndrome and death. Hoobler et al. (1952), however, did not observe any increase in toxicity with the use of digitalis in patients on protoveratrine treatment. We have encountered heart block and premature systoles.

## Electrocardiographic Changes

These are of two types; the acute changes induced by drug action and the more gradual return of the "left ventricular hypertrophy" or "left ventricular strain" patterns to a more normal voltage and shape in the course of treating hypertension.

Lovejoy et al. (1951) were impressed by the acute electrocardiographic changes, including T wave inversions, which sometimes occurred after administration of intravenous protoveratrine and which they regarded as evidence of coronary insufficiency

Elek, McNair and Griffith (1953), using veratrine intravenously, also describe inversion of T waves which were previously upright, especially in chest leads $V_4$ and $V_6$. They found no alteration in the blood potassium during the period of maximum hypotension. The absence of alteration in the blood potassium is of particular interest and merits repetition in view of the possibility mentioned earlier that sensitization to potassium ions may be responsible not only for the effect of most active veratrum alkaloids on amphibian striped muscle (Goutier, 1950) but also for some of the veratrum actions which occur in mammals. Release of potassium, if indeed it occurred, might explain some of the electrocardiographic changes.

effect may occur wh
and may have disa
before the blood press...
is seen after oral doses (Smirk and Chapman 1952).

Doyle and Smirk, (1953) also noted that the blood pressure fall after an intravenous injection of neogermitrine or protoveratrine may persist for 40 to 80 minutes after emesis and other discomforts have cleared.

The doses at which the various veratrum alkaloids first exhibit their hypotensive or emetic actions cover a wide range. Broadly speaking, the relationship between the hypotensive dose and the emetic dose appears to be preserved, provided the same route of administration is employed.

Emesis after veratrum alkaloids may be precipitated by food or even by a cup of tea [81, 324]. This may occur quite unexpectedly when the patient has been feeling comfortable previously. In some patients the vomiting occurs with singularly little distress; in others there is a period of misery and prostration. Some authors have suggested that veratrum preparations should be given after meals in the expectation that they would be less likely to produce toxicity. It seems rather probable from animal experiments that these alkaloids induce emesis by nervous stimulation (Fairbanks and Borison, 1951) and have no direct emetic action from stomach irritation (Swiss, 1952). When veratrum preparations are given after meals the reduced emetic action is accompanied by reduced hypotensive activity due to prolongation of absorption Doyle and Smirk (1953) thought that they got better results when the substance was administered before meals but in smaller doses. In this way the absorption and the results obtained were more predictable.

Retrosternal discomfort was sometimes even more distressing than the nausea and vomiting and some patients at the time were unable to swallow The cause of this sensation has not yet been worked out satisfactorily.

Various measures have been used in an attempt to counteract the emetic effect of veratrum alkaloids. Atropine and dramamine have had very little beneficial effect according to Barrow and Sikes (1951),

...es other
... 1 mg. of
atropine Symptoms arising from excessive blood pressure falls may be relieved by the horizontal posture and injections of neosynephrine or of ephedrine.

## Treatment of Hypertension with Veratrum Alkaloids

### Essential Hypertension

One of the first physicians to use veratrum alkaloids in the treat-

intravenously in doses sufficient to cause a substantial blood pressure fall, they are much less likely to cause side effects than are equally hypotensive doses given by mouth. An exception is that tingling and numb sensations and a generalized sensation of warmth spreading over the body is likely to be more prominent after a rapidly given intravenous dose — even one giving no other side effects (Doyle and Smirk, 1953).

It has been mentioned already that the margin between the hypotensive and the toxic dose often narrows with continued administration. Holley and Koffler (1950) made this observation using Vertavis, Mills and Moyer (1952) using Anatensol and Veriloid, and Smirk and Chapman (1952) found the same with Anatensol and Vertavis. Doyle and Smirk (1953) made the corresponding observation with protoveratrine and neogermitrine. In our experience most of the patients who seem stable and happy on one or other veratrum derivative for two or three months will be off treatment within twelve to eighteen months because adequate falls of blood pressure cannot be maintained without prohibitive toxic side effects. A reason why our experience is less favourable than some others is that, in our clinic, we have required that the trough of the blood pressure falls should be to near normal levels. Had we been content with blood pressure falls of 20 to 40 mm. systolic and 10 to 20 mm. diastolic it would have been possible to hold more on treatment. In our clinic we have been disappointed in that, having tried veratrum alkaloids in about 65 patients and gathering together 15 who gave useful blood pressure falls without significant toxicity, we have not managed to maintain an adequate response without important symptoms in any of them. These 15 patients were transferred to methonium treatment and have not desired to resume a veratrum régime.

For a time it was hoped that the toxicity of mixed veratrum alkaloid preparations would be eliminated by the removal from the mixtures of unfavourable substances responsible for toxicity; or that some pure derivative would be found having a substantial gap between the hypotensive and the toxic dose. The detailed study of many pure derivatives in man, reinforced by the work of Swiss (1952) in dogs, supports the contention of Krayer and Acheson (1946) that the emetic action is an integral part of the activity of the veratrum alkaloids. Clinical experience evidently runs rather closely parallel to the animal experiments and the likelihood of a separation of emetic and hypotensive activity in this group of drugs does not seem hopeful even among synthetic derivatives. An approach to this problem, which does not seem to have been explored sufficiently, is the question: why should the gap between hypotension and emesis be wider when veratrum drugs are given intravenously than when they are taken by mouth? It is also interesting in this connection that, after veratrum alkaloids, the toxic

We have also obtained improvements in retinopathy, breathlessness and headache and, on occasion, relief of anginal pain in our clinic during the initial phase of treatment when effective blood pressure control was practicable. The kind of improvement in high blood pressure cases is similar to that which follows effective methonium treatment or, indeed, any effective control over the blood pressure level which is therapeutically permissible.

### Nephritic Hypertension

In a limited experience with the use of veratrum derivatives in patients with nephritic hypertension we have not been able to distinguish any difference from the actions found in patients with essential hypertension. Hypertensive symptoms are relieved and the retinal picture improves if the blood pressure falls, but non-hypertensive manifestations are unchanged. It is desirable in every such patient to ensure that reduction of the blood pressure is not leading to additional nitrogen retention. Vomiting must not occur sufficiently often to upset the balance of water or protein metabolism.

### Eclampsia and Pregnancy Toxaemia

The use of veratrum preparations in eclampsia has never been entirely abandoned since the use in that disorder by Baker (1860). Results recently described by Assali (1950) in convulsive eclampsia suggest that veratrum alkaloids are of value in this condition. He is prepared to give veratrone by continued intravenous injection with a starting dose of 0.2 ml Recovery from coma may well be attributed to the measures taken The lesser toxicity of intravenous administration and the limited period for which the drug is required are favourable to its use in this condition.

Shapiro et al. (1952) and Assali et al. (1950) consider that veratrum viride has a strong effect on the blood pressure in the toxaemia of pregnancy, whereas tetraethylammonium chloride has a minor action. They report that, in contrast, patients with essential hypertension had very similar falls from the two substances. Failure to obtain a blood pressure fall with a ganglion blocking agent such as tetraethylammonium deserves further study We have had no difficulty in reducing the blood pressure in pregnancy toxaemia with hexamethonium bromide, but whereas our patients were sitting, Assali et al. (1950) had theirs recumbent.

### Comment on Veratrum Alkaloids

[illegible] with hypertension. Unfortunately, the effective

ment of essential hypertension was Collins (1915). Observations were also made by Hewlett (1917) and by Wedd (1925). In recent years even the most hopeful reports refer to the difficulties which arise from the proximity of hypotensive and toxic effects. Barrow and Sikes (1952) using Anatensol, found sustained falls in the absence of toxicity in 5/25 patients.

Freis (1951) felt that he could obtain fairly satisfactory results with Anatensol or Veriloid and a salt-poor diet. Coe, Best and Kinsman (1950) regarded their results with Vertavis as unsatisfactory. Gropper, Surtshin and Hedrick (1951) felt that they had failed to reproduce the beneficial effects from Veriloid claimed by other workers.

Smirk and Chapman (1952), using Anatensol or Vertavis in 36 patients, found 10 who had satisfactory falls of blood pressure without toxicity and could be maintained on treatment for three or more months. At the time it seemed that these 10 patients would remain well controlled, but this has not been so; one by one they have failed to exhibit adequate blood pressure falls without toxicity and the veratrum has been discontinued either at their own request or because it no longer had a sufficient effect. Other patients added to the series by Doyle and Smirk (1953) and treated in most instances with neogermitrine (a few with protoveratrine) have, subsequent to publication, exhibited the same sequence of events. It was noted, however, that patients with a low basal diastolic pressure could be better controlled in the initial phases and lasted longer on treatment.

Ruskin and Rider (1950) had already reported that the falls of blood pressure after Vertavis are greater in early labile cases, and Shapiro and Ferris (1952) also found that the degree of blood pressure fall could be correlated with the initial diastolic pressure and patients with the higher diastolic pressures showed a smaller percentage fall. Shapiro and Ferris (1952) reported that the percentage fall in normotensive subjects was approximately the same as it was in hypertensive subjects. This, they thought, suggested that the substance did not act on any particular hypertensive mechanism but on the nervous regulation of the blood pressure in an unspecialized sense. Kauntze and Trounce (1951) and Galen (1955) found Veriloid of limited use only, in essential hypertension.

It should be made clear that Hoobler et al. (1952) report satisfactory results with oral protoveratrine. They mention that, with protoveratrine treatment, orthopnoea patients have been able to lie flat, nocturnal dyspnoea has been prevented, headaches relieved and there has been improvement in retinopathy. Saphire (1954) also noted improvement in grade 4 retinopathy in 3 out of 6 patients and in 1 out of 3 grade 3 patients. Wilkins (1950) has described decrease of cardiac enlargement even in cases without congestive failure. Electrocardiographic patterns have improved and retinopathy has decreased.

## Experimental Pharmacology

There is some obscurity concerning the hypotensive action of hydralazine. It is evident from the literature that the following possibilities, which have been suggested, require a more detailed study.

1. That the hypotensive effect is due to an action on the central nervous system.
2. That there is a peripheral effect leading to dilatation of blood vessels.
3. That there is an adrenolytic, sympatholytic effect.
4. That release of histamine contributes to the blood pressure fall.
5. That it antagonizes certain pressor agents.

Unlike hexamethonium, the substance does not cause blockade of autonomic ganglia.

## Circulatory Effects of Hydralazine (Apresoline)

*Effect on the blood pressure.* — It is generally conceded that hydralazine induces falls of blood pressure in experimental animals. Craver and Yonkman (1950) found that the hypotensive action developed slowly in several species and Moyer et al. (1951) also found that, in dogs, intravenous injections of hydralazine induced a blood pressure fall which was only maximal about 30 minutes later. This suggested the possibilities of either metabolic alteration to an active compound or slow penetration to the site of action or slow response of the central mechanism [72]. There was a fall in peripheral resistance, tachycardia and increased cardiac output in the intact animal [174]. Walker et al. (1951) describe the occurrence of postural hypotension in dogs. Craver and Yonkman (1950) indicate that the increase in the cardiac output is not due to a direct cardiac stimulation as such action is not demonstrable in the isolated perfused cat's heart. Fall of blood pressure with increased cardiac output indicates a decrease of peripheral resistance. The increase in heart output is said not to occur if hexamethonium is given beforehand to block autonomic actions. Schroeder (1952b) states that once the hypotensive effect has been obtained by hydralazine, further injections do not lower the blood pressure.

The blood pressure fall may be due to a central action (Gross, Druey and Meier, 1950; Craver and Yonkman, 1950). Craver, Barrett, Cameron and Yonkman (1951) find that hydralazine produces comparatively small falls of blood pressure in spinal animals even when their blo[illegible]
contribu[illegible]
In two c[illegible]
head, Grimson, Orgain, Rowe and Sieber (1952) failed, however, to demonstrate a central site of action.

hypotensive and the toxic doses are close and the use of these drugs requires careful adjustment of the dose and of the conditions of administration.

Most writers agree that, with continued administration, the gap between the therapeutically effective dose and the toxic dose narrows, so that patients who have done well for a time often need to abandon the drug. This has been our experience.

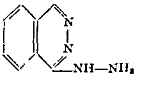
In severe hypertensive patients we were only able to maintain good falls of blood pressure (to near normal) for a year or more in a very few out of 80 patients, and these ultimately desired to change to other drugs. In this we repeat the experience of many others who have attempted to use veratrum alkaloids therapeutically. Some physicians, however, have been more favourable to veratrum. To some extent the difference of opinion seems to depend upon whether the investigator treats mild hypertensives, and on whether in severe hypertensive patients such blood pressure reductions as 20 to 30 mm. Hg systolic, 10 to 15 mm. Hg diastolic are considered acceptable. Such small falls of blood pressure are easier to obtain without toxicity, but without control tests using inert substances it may be difficult to distinguish these small reductions from the blood pressure falls which occur with placebos.

We feel confident that reductions of the blood pressure to near normal levels, in severe hypertension, can rarely be maintained by the use of veratrum alkaloids, and consequently the degree of objective and subjective improvement in severe hypertensives is much less with veratrum alkaloids than with other methods of treatment which are now available.

The veratrum drugs are, however, of great theoretical interest. By meticulous adjustment of the dose, using slow intravenous administration, the blood pressure can usually be reduced to normal levels without causing discomfort. A drug with a similar action to veratrum but with a much wider gap between the hypotensive and toxic doses would be most useful

## HYDRALAZINE (1-HYDRAZINOPHTHALAZINE, APRESOLINE)

It was shown by Gross, Druey and Meier (1950) and Craver and Yonkman (1950) that a group of phthalazine derivatives produce a sustained depressor action in experimental animals. 1-hydrazinophthalazine (hydralazine) is one of the more potent of these



is that the flow through *these* vessels is much influenced by the state of activity of the heart muscle.

It is thought that the hydralazine is to some degree adrenolytic[254]. Experiments in animals show that the effect of adrenaline is reduced after hydralazine has been given, but it is usually thought that hydralazine does not entirely abolish the action of adrenaline or of noradrenaline; and also that reversal of the pressor action of noradrenaline is not a result of hydralazine administration. Moyer, Handley and Huggins (1951), on the other hand, report experiments in dogs in which intravenous injections of 1 or 2 mg./kg. of hydralazine blocked the pressor action of adrenaline and noradrenaline and caused adrenaline reversal.

Finally there is evidence that hydralazine acts as a histamine-releasing agent, which is explained by it acting as an antihistaminase.

## Other Pharmacological Effects

the intestines of th ses of the nictitating membrane of the cat to drenaline are unaffected[48]. Proosdij-Hartzema and De Jongh (1955) found that hydralazine reduced the blood pressure of rats with experimental hypertension.

It is of great interest that Comens (1956) induced a condition closely resembling disseminated lupus erythematosus when normotensive dogs were given 200 mg. hydralazine daily, by mouth.

## Clinical Studies with Hydralazine (Apresoline)

### Oral and Parenteral Dosage

Hydralazine has been used intramuscularly for clinical investigations

times daily. The dose is raised gradually daily or at intervals of several days until a hypotensive action is obtained. We found, as most other observers have done, that a degree of drug toleration develops with repeated administration. This makes further increases in the dose necessary later, to maintain the hypotensive action The total daily dose usually rises to between 200 and 800 mg. but as much as 1400 mg. has been given Tablets of hydralazine (Apresoline) are manufactured in 10, 25 and 50 mg sizes. They are administered after meals.

### Hypotensive Action

The doses ordinarily used for the treatment of hypertension produce falls of blood pressure which are in excess of those induced by placebos.

Taylor, Page and Corcoran (1951) find that hydralazine inhibits the blood pressure increase which ordinarily follows stimulation of the central end of the vagus nerve. These workers also reported that the blood pressure rise from serotonin was inhibited but not that from renin, angiotonin or pitressin. Yonkman (1953) also found that hydralazine antagonized the action of serotonin: Renzi et al. (1954) and Yonkman (1953), however, found that it also antagonized angiotonin.

Schroeder (1952b) considers that hydralazine abolishes the pressor action of both pherentasin and angiotonin. He considers this as important in so far as a humoral pressor mechanism in chronic hypertension may be inhibited. He states that hydralazine also appears to act upon an area of the brain, either at medullary levels or at the hypothalamus. He thinks that some basic circulatory mechanism overactive in hypertension is inhibited by this substance. Schroeder considers that pherentasin is the only pressor substance consistently found in hypertensive blood which is absent from normotensive blood. The hypotensive effect in normotensives would seem to show that Schroeder's explanation of the blood pressure fall in hypertension is unlikely to be the sole explanation for blood pressure reduction.

*Effect on the kidneys.* — An increase in the renal blood flow in experimental animals has been reported [101, 171, 176]. The increase in renal blood flow was approximately parallel to the increase in cardiac output and took place although the blood pressure was reduced. The urine volume consistently decreased although there was no decrease of glomerular filtration.

*The peripheral action.* — The blood flow in the perfused hind limb of the rabbit is uninfluenced by hydralazine (Craver, Barrett, Cameron and Yonkman, 1951). A corresponding result was obtained by Moyer, Handley and Huggins (1951) who found that in dogs an intra-arterial injection of 0.1 to 0.2 mg./kg. did not decrease the peripheral resistance in the leg. On the other hand, Bein, Tripod and Meier (1952) reported that when perfused through the rabbit's and cat's heart *in situ*, hydralazine was able to overcome coronary constriction induced by posterior pituitary hormone (and so also does histamine).

Evidently there is some conflict of evidence as to whether there is or is not a direct effect of hydralazine on blood vessels. The reactions of peripheral vessels to hypotensive agents depend to an important degree on whether such vessels possess sufficient tone to be able to exhibit dilatation. Were there a clear demonstration that a peripheral vasodilatation does not take place with hydralazine the evidence for a central location of the site of action would be strengthened. It would be necessary to show that the blood vessels were capable under the same experimental conditions of showing unmistakable dilatation in response to known peripheral vasodilators. A difficulty in using coronary vessels for evidence of a direct action on blood vessels at the periphery

is that the flow through these vessels is much influenced by the state of activity of the heart muscle.

It is thought that the hydralazine is to some degree adrenolytic [254]. Experiments in animals show that the effect of adrenaline is reduced after hydralazine has been given, but it is usually thought that hydralazine does not entirely abolish the action of adrenaline or of noradrenaline; and also that reversal of the pressor action of noradrenaline is not a result of hydralazine administration. Moyer, Handley and Huggins (1951), on the other hand, report experiments in dogs in which intravenous injections of 1 or 2 mg./kg. of hydralazine blocked the pressor action of adrenaline and noradrenaline and caused adrenaline reversal.

Finally there is evidence that hydralazine acts as a histamine-releasing agent, which is explained by it acting as an antihistaminase.

### Other Pharmacological Effects

Hypotensive doses appear to have little action on the intestines of the dog or on the uterus of the cat *in vivo*. The responses of the nictitating membrane of the cat to adrenaline and noradrenaline are unaffected [46]. Proosdij-Hartzema and De Jongh (1955) found that hydralazine reduced the blood pressure of rats with experimental hypertension

It is of great interest that Comens (1956) induced a condition closely resembling disseminated lupus erythematosus when normotensive dogs were given 200 mg. hydralazine daily, by mouth.

## Clinical Studies with Hydralazine (Apresoline)

### Oral and Parenteral Dosage

Hydralazine has been used intramuscularly for clinical investigations in doses of 10 to 20 mg. Such doses usually reduce the blood pressure and may induce side effects. Therapeutic doses are almost invariably given by mouth starting with initial doses of 10 to 25 mg. three or four times daily. The dose is raised gradually daily or at intervals of several days until a hypotensive action is obtained. We found, as most other observers have done, that a degree of drug toleration develops with repeated administration. This makes further increases in the dose necessary later, to maintain the hypotensive action. The total daily dose usually rises to between 200 and 800 mg. but as much as 1400 mg. has been given. Tablets of hydralazine (Apresoline) are manufactured in 10, 25 and 50 mg. sizes. They are administered after meals.

### Hypotensive Action

The doses ordinarily used for the treatment of hypertension produce falls of blood pressure which are in excess of those induced by placebos.

Taylor, Page and Corcoran (1951) find that hydralazine inhibits the blood pressure increase which ordinarily follows stimulation of the central end of the vagus nerve. These workers also reported that the blood pressure rise from serotonin was inhibited but not that from renin, angiotonin or pitressin. Yonkman (1953) also found that hydralazine antagonized the action of serotonin: Renzi et al. (1954) and Yonkman (1953), however, found that it also antagonized angiotonin.

Schroeder (1952b) considers that hydralazine abolishes the pressor action of both pherentasin and angiotonin. He considers this as important in so far as a humoral pressor mechanism in chronic hypertension may be inhibited. He states that hydralazine also appears to act upon an area of the brain, either at medullary levels or at the hypothalamus. He thinks that some basic circulatory mechanism overactive in hypertension is inhibited by this substance. Schroeder considers that pherentasin is the only pressor substance consistently found in hypertensive blood which is absent from normotensive blood. The hypotensive effect in normotensives would seem to show that Schroeder's explanation of the blood pressure fall in hypertension is unlikely to be the sole explanation for blood pressure reduction.

*Effect on the kidneys.* — An increase in the renal blood flow in experimental animals has been reported [101, 174, 176]. The increase in renal blood flow was approximately parallel to the increase in cardiac output and took place although the blood pressure was reduced. The urine volume consistently decreased although there was no decrease of glomerular filtration.

*The peripheral action.* — The blood flow in the perfused hind limb of the rabbit is uninfluenced by hydralazine (Craver, Barrett, Cameron and Yonkman, 1951). A corresponding result was obtained by Moyer, Handley and Huggins (1951) who found that in dogs an intra-arterial injection of 0.1 to 0.2 mg /kg. did not decrease the peripheral resistance in the leg. On the other hand, Bein, Tripod and Meier (1952) reported that when perfused through the rabbit's and cat's heart *in situ*, hydralazine was able to overcome coronary constriction induced by posterior pituitary hormone (and so also does histamine).

Evidently there is some conflict of evidence as to whether there is or is not a direct effect of hydralazine on blood vessels. The reactions of peripheral vessels to hypotensive agents depend to an important degree on whether such vessels possess sufficient tone to be able to exhibit dilatation. Were there a clear demonstration that a peripheral vasodilatation does not take place with hydralazine the evidence for a central location of the site of action would be strengthened. It would be necessary to show that the blood vessels were capable under the same experimental conditions of showing unmistakable dilatation in response to known peripheral vasodilators. A difficulty in using coronary vessels for evidence of a direct action on blood vessels at the periphery

*therefore* a decrease in the cerebral vascular resistance. Kleh and Fazekas (1954), whose observations were made on elderly patients, found that the cerebral blood flow was increased.

## Renal Circulation

The fall in blood pressure after hydralazine in man, as in animals, is marked by an increase of the renal blood flow (Reubi, 1950). Mackinnon (1952) found the renal blood flow increased in hypertensives, and Kirkendall and Culbertson (1952) and Wilkinson et al. (1952) found it increased in both 2 normotensive and 2 hypertensive patients. There was no unfavourable effect on the glomerular filtration rate. Evidently renal vasodilatation occurs. In cases of acute nephritis studied by McCrory and Rapoport (1952), increased renal blood flow was accompanied by a decrease in the volume of urine excreted. Van der Kolk, Dontas and Hoobler (1954) confirmed the increase in renal plasma flow from initial doses of hydralazine but found that this effect passed off with continued treatment. Drug toleration was exhibited concurrently to the hypotensive action.

## Limb Circulation

tant and deserves repetition. It differs somewhat from the results obtained in experimental animals.

Most authors agree that hydralazine warms the skin of the extremities and sometimes causes facial flushing and conjunctival injections [66, 72, 99, 128]. Similar observations were made in our clinic. Freis et al. (1953) also noted a slight decrease in the blood flow through muscles and a marked increase in the estimated hepatic portal blood flow.

## Adrenolytic Action

Some authors are unimpressed by the adrenolytic action of hydralazine. It was pointed out by Moyer (1953) that hydralazine given to a patient with phaeochromocytoma led to an initial fall of blood pressure followed by a substantial hypertensive crisis; an unexpected result had the substance been strongly adrenolytic. Freis and Finnerty (1950) found that moderate doses of hydralazine did not prevent or reverse the pressor action of adrenaline given by slow intravenous injection. They considered that there was partial inhibition of sympathetic reflexes; an action which they thought was most likely to be located in the central nervous system.

When injected intravenously, hydralazine does not produce an immediate effect. There is a delay of minutes before the first distinctive fall of blood pressure takes place.

Wilkinson, Backman and Hecht (1952) using cardiac catheterization observed an average increase of 110 per cent in the cardiac output in 4 normotensive patients after hydralazine. In 2 patients with hypertensive heart disease who had previously been in heart failure there was a smaller rise in the cardiac output. In normal subjects the intravenous administration of hydralazine usually increased the pulse pressure but did not always decrease both systolic and diastolic blood pressure. In hypertensives intravenous administration gave a good fall in the systolic and diastolic pressure, usually with an increase in the pulse pressure.

Assali and co-workers (1952), using the ballistocardiograph observed increases of the cardiac output in hypertensive pregnant women. Freis et al. (1953) also found an increase of the cardiac output in 6 hypertensive patients by a cardiac catheterisation technique, and they reported also an increase of the hepatic portal blood flow and a slight decrease of the blood flow through the muscles of the calf. According to Moyer (1953) the cardiac output returns to control levels after about one month of treatment with the drug, but at this time the blood pressure was likewise returning towards the original level; so apparently, this was merely due to the development of drug toleration. The pulse rate was usually increased. It is evident that a fall of blood pressure associated with an increase of cardiac output must be attributed to decrease of the peripheral resistance.

Johnson, Freis and Schnaper (1952) noted tachycardia in all patients in whom hypotension had been induced, and some patients complained of palpitation. Postural hypotension was usually mild in degree. Moyer (1953) also noted some postural hypotension. Like many other hypotensive agents hydralazine has a greater effect on patients whose blood pressures are high than on those whose blood pressure elevation is moderate. Schroeder (1952a) found the hypotensive effect was also greater in patients who had had a sympathectomy or had been on a salt restriction diet. Taylor et al. (1952), however, did not think that sympathectomy altered the response to hydralazine.

The abolition or reduction of the Valsalva vasopressor overshoot, of the tilt back overshoot and of the cold pressor reflex has been reported by Freis and Finnerty (1950). This suggests some form of interference with sympathetic reflexes.

## Cerebral Circulation

Hafkenschiel and Friedland (1953) found that following the administration of hydralazine the cerebral blood flow was not altered to any important degree during the blood pressure reduction. There is

Johnson (1953) reported that 17 out of 40 of his hypertensive patients had important decreases in the blood pressure to levels which

cy. Most of the successful cases were mild hypertensives. Hoobler (1951) found exceptional patients who maintained good hypotensive responses on continued administration. Johnson, Freis and Schnaper (1952) considered that hydralazine alone had no lasting hypotensive effect. They found sustained action in only 3 of 17 patients under treatment with this substance alone. Shapiro and Grollman (1953), Grimson et al (1950) and Wald et al. (1953) failed to demonstrate sustained blood pressure falls on repeated administration.

Falls of blood pressure do not always precede the development of toxic manifestations and Kahn (1953) reports that in some patients the blood pressure falls pass off with continued administration. Citing results with 12 patients he was unable to maintain persistence of the blood pressure reduction without unpleasant side effects. We also had this experience.

Moyer (1953) was dissatisfied with the results obtained with hydralazine alone. He says: "Although the initial results look somewhat encouraging, after one year only 9 of the 52 patients continue to take the drug and of these 9, only 5 have continued to maintain a significant reduction in mean blood pressure (excess of 20 mm., or below 150 mm. systolic and 100 mm. diastolic). In the remaining four, tolerance apparently had developed and side reactions occur when the drug is increased in an attempt to further reduce the blood pressure". Moyer (1953) considers that hydralazine alone gives results approximately equivalent to those from veratrum extracts and both are inferior to hexamethonium alone. "Dibenzyline", which blocks peripherally, gives better initial results which fall off and the long term results are no better than hydralazine.

Assali and Suyemoto (1952) find hydralazine more satisfactory

... pregnancy toxaemia.

## Side Effects of Hydralazine (Apresoline)

The side effects of hydralazine are numerous. The extent to which they occur depends on whether an attempt has been made to induce a substantial fall of blood pressure by hydralazine alone or whether hydralazine has been given in combination, and on the duration of administration. Some side effects such as ...

... sappear with

... r appearance

... ssening of side

## Treatment of Hypertension with Hydralazine (Apresoline)

Page (1951) has stated that on oral doses good effects may take 10 days or more to develop. Out of 70 patients, 33 had a fall of 20 or more mm. Hg diastolic. He observed clear reversal of the syndrome of malignant hypertension in several patients. Taylor et al. (1952) used hydralazine, raising the dose as high as they could, in order to secure as much blood pressure reduction as was practicable. In most instances they obtained falls of blood pressure. The side effects were substantial but they tended to be reduced with continued administration. The benefits which they reported were reduction in diastolic pressure and decrease in severe headache, dizziness and retinal haemorrhages. At the same time they report a lack of improvement in the cardiac status and in some instances the cardiac condition was worsened. Angina and cardiac infarction were encountered. It would seem that these adverse effects are attributable to the increased rate and output of the heart. Taylor et al. (1952) mention that digitalization and sodium restriction are used by them as adjuncts to treatment with hydralazine. The authors appear to favour the use of this substance but the results which they give are much inferior to those which can be obtained by a well-controlled methonium régime.

Hafkenschiel and Lindauer (1953) have made a 2-year study of the use of hydralazine in the treatment of hypertension. They found among the more severe types of hypertension only 1 in 7 individuals had a reduction in the blood pressure which they considered to be favourable. They accepted as favourable such blood pressure reductions as from 120 mm. Hg in the diastolic pressure to 110 mm. Hg or lower on at least 2 outpatient visits. A depressor response was obtained using this criterion in 57 per cent of hypertensive patients of the milder type who took the drug for at least 1 year. Some of their results, however, were obtained with the use of hydralazine in conjunction with salt restriction. No patients were observed to have a reduction in heart size as indicated by decrease in frontal surface area of 30 per cent plus a decrease in transverse cardiac diameter more than 3 cm., and only 4 patients were observed to have improvement in retinopathy, only 1 of these being in group 3. The authors are prepared to recommend the use of hydralazine in patients with severe essential hypertension who have good renal, cardiac and retinal findings, persisting with this treatment so long as there is no evidence of progression. It seems evident from this paper that a certain amount of benefit may be obtained by the use of this substance in carefully selected patients. Compared with other methods of treatment which are available, it appears that the results obtained with hydralazine alone are poor. For example, only 4 out of 40 patients showed retinal improvement and 6 showed advance in retinopathy.

even resembling acute rheumatoid arthritis. Other so-called collagen diseases made their appearance as, for example, a condition closely resembling disseminated lupus erythematosus. Febrile attacks occurred which did not appear to be due to infection. Usually some anaemia develops (Perry and Schroeder, 1954). Among the toxic side

TABLE XVI 4. *Side effects due to 1-hydrazinophthalazine (Apresoline) in the treatment of essential hypertension (benign) in forty patients classified into Group 1 (successful results), Group 2 (partly successful results), and Group 3 (unsuccessful results)*

(Johnson, R. P. Amer. Heart J., 46: 593, 1953)

| Symptoms | Group 1 17 patients | Group 2 9 patients | Group 3 14 patients | Total 40 patients | |
|---|---|---|---|---|---|
| | No. | No. | No. | No | % |
| None | 4 | 0 | 0 | 4 | 10 |
| Headache | 9 | 8 | 13 | 30 | 75 |
| Palpitation | 4 | 3 | 5 | 12 | 30 |
| Tachycardia | 2 | 2 | 5 | 9 | 23 |
| Flushing | 4 | 1 | 4 | 9 | 23 |
| Weakness | 3 | 1 | 5 | 9 | 23 |
| Tingling or numbness | 3 | 3 | 2 | 8 | 20 |
| Tremor | 1 | 1 | 6 | 8 | 20 |
| Dizziness | 3 | 2 | 1 | 6 | 15 |
| Nausea | 4 | | 2 | 6 | 15 |
| Vomiting | 3 | | 1 | 4 | 10 |
| Swelling of ankles | 2 | | 2 | 4 | 10 |
| Drowsiness | 1 | 2 | 1 | 4 | 10 |
| Chilliness | 1 | | 2 | 3 | 8 |
| Dry mouth | | 1 | 2 | 3 | 8 |
| Sweating | | | 3 | 3 | 8 |
| Swelling periorbital | | | 2 | 2 | 5 |
| Stiffness | 1 | | 1 | 2 | 5 |
| Chill and fever | | | 1 | 1 | 3 |
| Arthritic hand | 1 | | | 1 | 3 |
| Insomnia | | | 1 | 1 | 3 |

effects observed by Taylor et al. (1952) were arthralgia, myalgia and fever. A case of pancytopenia with purpura, but with eventual recovery, was described by Kaufman (1952) following seven months' treatment. Paraesthesias and hyperaesthesias may develop (Moyer, 1953) and increase with continued administration. Myocardial infarction has been described, occurring about 20 minutes after the drug (Moyer, 1953). In 2 cases of the series of 40 reported by Johnson (1953)

effects was associated with decrease in hypotensive action and was due to drug toleration. An increase of dose, sufficient to restore the action on the blood pressure, also caused the reappearance of side effects. Most authors agree that gradual increase of the dose decreases the severity of side effects. Wilkins (1953) has avoided severe headaches by starting with as little as 10 mg. Tachycardia is almost invariably present (Assali and Suyemoto, 1952), and does not occur solely in patients who have a good fall in blood pressure Not infrequently the cardiac status deteriorated [212]. However, Judson et al. (1956) noted improvement in the circulatory and renal functions in congestive heart failure.

There is often considerable flushing, injection of the conjunctiva, lachrymation and peripheral oedema. Stuffiness of the nasal mucous membrane may occur and not infrequently severe headache. These side effects are sometimes attributed to the release of histamine [218], and may be greatly lessened by antihistaminics [106, 198, 218, 225, 242]. We also noted a decrease in side effects with antihistaminics and in our series this was associated with concurrent decrease in hypotensive action. Nausea, vomiting and diarrhoea occur in certain patients [172, 219, 242].

A patient who developed a hypotonic urinary bladder, with difficulty in micturition, was described by Goldstein, Schloss and Cohn (1952). There was decrease in the maximum voiding pressure. The disturbance disappeared when the drug was stopped. Laurence and Miles (1953) reported bladder paralysis with distension on an oral dose of 25 mg. of hydralazine 6-hourly. This recovered within 24 hours after withdrawal of the drug Bladder sensation was unaffected.

A severe mental reaction has been reported (Moser et al., 1953) but recovery took place within 24 hours. These authors also report transient euphoria and attacks of nervousness. Schroeder (1952a) refers to 2 mentally depressed patients who became comatose. Stunkard et al. (1954) also reported a psychosis which cleared on withdrawing the drug.

Johnson (1953) gives a table setting out the side effects encountered in a series of 40 patients (Table XVI 4). Kvale (1956) considers that the side effects of hydralazine including collagen disorders are reversed by stopping the drug.

A chemical relative of hydralazine (Nepresol) has been studied pharmacologically by Bein et al. (1953). According to Essellier et al (1953), Kummer and La Rosée (1953) and Franke and Thiele (1953) Nepresol leads to somewhat fewer side effects than hydralazine.

### Delayed Poisoning by Hydralazine (Apresoline)

Certain toxic effects may develop with continued administration. Morrow, Schroeder and Perry (1953), for example, report that 16 out of 250 patients developed a considerable degree of aching pain in joints,

ergotamine, dihydroergocristine, dihydroergokryptine and dihydroergocornine. A mixture of the last three alkaloids is employed clinically under the name Hydergine.

## Experimental Pharmacology

Much of the work on the hypotensive action of dihydrogenated ergot alkaloids comes from Swiss workers. Rothlin and Cerletti (1950b) state that the pharmacological actions of ergot alkaloids and of the dihydrogenated derivatives involve the following components:

1. Actions brought about through the central nervous system:

(a) A blood pressure reduction of central nervous origin due to inhibition of vasomotor or stimulation of vasodilator neurones.

(b) Depression of certain circulatory reflexes, e g. the carotid sinus reflex, through an action on a reflex centre located in the central nervous system.

(c) Slowing of the heart through activation of the heart slowing centre; alternatively, inhibition of the accelerating centre.

2. Peripheral actions:

(a) A peripheral adrenolytic and sympatholytic action.

(b) A direct stimulus to the muscle of blood vessels leading to vasoconstriction.

When the natural ergot alkaloids undergo dihydrogenation the direct stimulating action on muscle is much diminished.

## Circulatory Effects of Dihydrogenated Ergot Alkaloids

*Effect on the blood pressure*

The central nervous system action. Rothlin (1946a) noted that the dihydrogenated ergot alkaloids usually had a powerfu. hypotensive action in the anaesthetized cat, but not in the spinal cat[203]. A similar observation, using dihydroergocornine, was made by Bluntschli and Staub (1949). When the central nervous system was destroyed, as in the pithed cat, the dihydrogenated ergot alkaloids, as well as the natural alkaloids, always raised the blood pressure. This latter effect is due to another action — namely, the stimulating action of the alkaloids directly upon the smooth muscle of blood vessels. The blood pressure rises in the pithed cat in conjunction with the apparent absence of any *direct* action on the heart, suggest strongly that the falls of blood pressure which occur in the whole animal are of central nervous origin, due to inhibition of the vasomotor centre or stimulation of a vasodilator centre. Further evidence of a central effect has been obtained by the intracisternal injection of ergotamine, which produces a striking fall in the blood pressure[251].

An additional study on localization is reported by Konzett and

coronary insufficiency was made worse. Symptoms of myocardial ischaemia are probably related to increase of heart rate and output together, sometimes, with excessive hypotension. Judson et al. (1956) also find that increases of cardiac output and pulse rate are concerned when angina is caused by hydralazine.

### Comment on Hydralazine (Apresoline)

Sufficiently large doses of hydralazine almost always reduce the blood pressure but these effective doses often cause distress from side effects. With continued administration side effects lessen, but concurrently the hypotensive action is also lost in many patients. We suspect in many instances where patients are taking hydralazine without side effects that the dose is subthreshold and the hypotensive action is not pharmacological, but represents a placebo type of action. In some instances modest falls of blood pressure due to drug action persist in the absence of side effects. Continued administration of hydralazine has led to delayed toxicity, the patients developing disorders which resemble rheumatoid arthritis and disseminated lupus erythematosus. Few clinics now approve of hydralazine as the sole means of reducing the blood pressure, but as will be seen later its use in combination with hexamethonium or pentolinium has some advocates. We have abandoned the use of hydralazine in our clinic, mainly on account of the severity of immediate side effects and the occurrence of delayed toxicity.

## DIHYDROGENATED ERGOT ALKALOIDS

Some observations on the circulatory effects of ergot were made as far back as 1884 by Kobert. Dale (1906) was the first to recognize that ergot alkaloids had two effects: a stimulation of plain muscle and a "specific paralysis of the motor elements in the structures associated with sympathetic innervation". Following the synthesis of the dihydrogenated derivatives of four ergot alkaloids by Stoll and Hofmann (1943), it was soon recognized that dihydrogenation involved decrease of the stimulating effect upon plain muscle. This modification in the pharmacology had clinical interest: whereas the unmodified ergot alkaloids raised the blood pressure, the dihydrogenated alkaloids reduced it.

According to Rothlin (1946a) there are six natural alkaloids of ergot each occurring in two isometric forms (-ine and -inine), for example, ergotamine and ergotaminine; the latter forms being of little pharmacological interest. The -ine forms of the alkaloids are: ergotamine, ergosine, ergocristine, ergokryptine, ergocornine and ergobasine. Four dihydrogenated derivatives have been studied, namely, dihydro-

is supported by the fact that r ... responses to chemical stimulation persist even when the baroce; ... dihydrogenated alkaloids[237]. ... respiratory or vasomotor response to hypoxaemia, carbon dioxide inhalation, or potassium cyanide. The experiments, however, were performed on cats and Comroe (1939) thinks that in the cat the carotid body chemoreceptors are only moderately important in comparison with the aortic receptors.

**The peripheral action.** The natural and dihydrogenated ergot alkaloids have two peripheral actions on blood vessels, one of which is the direct stimulating action on muscle referred to above, the other is a sympatholytic-adrenolytic action. With the natural alkaloids the direct action on the muscle of blood vessels is much stronger; in the whole animal it is often the predominant action, causing blood pressure rises, and it is responsible for the peripheral gangrene of ergot poisoning and has limited the clinical employment of the natural alkaloids.

The dihydrogenated ergot alkaloids possess both of the peripheral actions referred to above, but of these the direct vasoconstrictive action is weak and is overcome in the whole animal by the more powerful vasodilator actions. It is only when these vasodilator actions are prevented that vasoconstriction occurs. The vasoconstriction can be seen on perfusion of the blood vessels of the rabbit's ears and in the frog's limbs and also in isolated strips of arteries from cattle[201].

predominates, and the result is vasoconstriction. If, however, the intra-arterial injection is made into a leg when the blood vessels are innervated vasodilatation occurs, because under these conditions the sympatholytic action is more important than, and overcomes, the direct action on the muscle of blood vessels[131].

Just as the demonstration of a sympatholytic effect requires first that impulses should be passing down the efferent pathways of the sympathetic, so the blood vessels must be under the action of adrenaline before one can demonstrate the adrenolytic action of a drug. All ergot alkaloids, natural and synthetic, except ergobasine (ergometrine) inhibit or reverse the action of adrenaline[201].

A good illustration of the adrenolytic action is seen when the intravenous administration of adrenaline is used to raise the peripheral vasomotor tone in the spinal cat; the dihydrogenated ergot alkaloids then produce a fall of blood pressure[203].

Schneider and Wiemers (1951) find that Hydergine, when given in the dog under ordinary circumstances, does not decrease the resistance of the cerebral circulation; but if the cerebral blood vessels are first constricted by hyperventilation, then Hydergine decreases the re-

Rothlin (1953). When vasomotor impulses are interrupted by cutting the spinal cord of a cat at the level of the first cervical vertebra and destroying the medulla, the dihydrogenated ergot alkaloids are no longer able to produce a fall of blood pressure and, in fact, produce a rise by direct stimulation of the muscle of blood vessels. This latter action is not observed when nervous connections are intact, for then the more powerful hypotensive action of central nervous origin predominates.

It was noted that in the cat, following low decerebration, the administration of dihydroergocornine or Hydergine led to a blood pressure fall in the great majority of experiments. The central nervous action of these alkaloids is evidently not dependent upon parts of the brain lying above the medulla.

In the decerebrate cat the hypotensive action persists after section of the spinal cord at T7, but if the section is made at C6 or T1 the blood pressure sometimes falls. It seems, therefore, that an important part of the central hypotensive action of these dihydrogenated ergot alkaloids is medullary, and that the pathways concerned (vasoconstrictor or dilator) leave in the upper part of the spinal cord; some of them, apparently, between T1 and T7. The pathways can be interrupted by section at C1.

Further evidence [138] that the predominant hypotensive action is of central nervous system origin comes from experiments in which the efferent discharge from the centres is blockaded by tetraethylammonium. During such ganglionic blockade the anaesthetized, intact cat, and the decerebrate cat in most instances, and the spinal cat in all instances, exhibited blood pressure rises of peripheral origin in response to dihydrogenated ergot alkaloids.

The action on baroceptive reflexes from the carotid sinus. Bircher and Cerletti (1949), in an article in Kappert's

alkaloids. This action is also of central nervous origin. Doses of alkaloids which have no clearcut peripheral adrenolytic effect inhibit the carotid sinus pressor reflexes.

Sutton, Cerletti and Taeschler (1950), in a study made of the effect of the separate dihydrogenated ergot alkaloids and of Hydergine on the carotid sinus stretch reflex, also found in the cat that they caused inhibition. Dihydroergocristine has a particularly strong action.

The inhibition of certain vasomotor reflexes by ergotoxin was first described by Rothlin (1923), and a similar finding was obtained by Heymans and Regniers (1929). Wright (1930) was able to show that this action was located in the central nervous system. Wright (1930) and also Von Euler and Schmiterlöw (1944) suggest that the effect is chiefly on the afferent side of the reflex arc within the brain. This idea

[illegible] 10 to [illegible] re en- [illegible] countered occasionally. The blood pressure falls were usually [illegible] and to be greater in hypertensives than in normotensives [85, 110, 277]. A number [illegible] potential blood pressure falls following [illegible] the blood pressure fall usually occurs within [illegible] persists for 1 to 2 hours [22].

Reports concerning the effect upon the blood pressure of oral doses of dihydrogenated ergot alkaloids are conflicting, but all are agreed that the falls a[illegible] than those induced by intravenous injection. Authors who m[illegible] cluded that the blood pressure [illegible] are small [22, 25, 85, 120, 152, 236]; but there have been reports also of falls of blood pressure from oral Hydergine which exceeded appreciably the falls associated with placebo administration [84, 262].

Some authors who consider oral Hydergine reduces the blood pressure remark that the hypotensive effect is more evident in mild, labile cases than in advanced hypertensive states [84, 261]. Others [22, 25, 62, 112, 278, 277] have recorded their clinical impressions that the degrees of blood pressure reduction from oral administration are small.

Moister et al (1949) observed a toleration to the blood pressure reducing effect of Hydergine and of dihydroergocornine. Using oral administration we also observed a degree of drug toleration to the hypotensive action, but not to the heart slowing effect.

### Hypotensive Action

All are agreed that there is a reduction in the heart rate, often of 10 to 20 beats per minute, after effective hypotensive doses of the various dihydrogenated ergot alkaloids and Hydergine. The effect is probably vagal as it is antagonized by atropine.

Kappert (1949) says that prolonged administration of Hydergine leads to an increase in the cardiac output. Freis et al. (1949b) found the cardiac output unchanged or slightly increased. Wilkins et al. (1949) reported no great change. Hauss et al. (1949b) sometimes observed increases and sometimes decreases.

A fall in output was reported by Delius, Hammerschmidt and Odenthal (1949), Zickgraf (1949), Werko and Lagerlöf (1949), Hauss, Kreuziger and Asteroth (1949), Blumberger (1950) and Volker and Kaczmarek (1950)

It is not unlikely that the conditions of the investigation influence the result obtained For example, with a sympatholytic agent a fall in cardiac output is more likely to occur with the patient in the sitting than in the lying posture.

sistance of the cerebral blood vessels and augments the flow through the brain considerably.

*Effect on the heart.* — At rest the heart rate in animals is decreased by the hydrogenated ergot alkaloids [131, 200].

Rothlin (1945, 1946a) showed that in the isolated heart-lung preparation, cat or dog, neither the natural nor the dihydrogenated ergot alkaloids have any effect, either sympatholytic or adrenolytic, on the heart action; neither the frequency, nor the rhythm, nor the output is affected. Such evidence makes it clear that as the heart slowing is not a peripheral sympatholytic effect directly on the heart, it is likely to be due to some central nervous action: either the increased activity of the vagal centre or decreased activity of the sympathetic accelerator centre. A suggestion that the slowing is vagal comes from the ability of large doses of atropine to prevent the pulse slowing action of ergotamine in almost all cases [205].

*Other pharmacological effects* — There is evidence that the respiratory centre is depressed and respiration slows [202, 111]. Other evidences of central nervous system depression are: increase in the sedative action of morphine and reduction in the movement of so-called "waltzing mice" [204]

Rothlin (1946a) showed that the dihydrogenated alkaloids differ from the natural alkaloids in that they do not stimulate the uterus Indeed, dihydroergocristine inhibits the increase in tone of the isolated rabbit uterus ordinarily obtained by the action of adrenaline. The adrenolytic action of the dihydrogenated ergot alkaloids may be further demonstrated on the isolated seminal vesicle of the guinea-pig, by prevention or reduction of the inhibitory action of adrenaline on the rabbit intestine, and by inhibition of the hyperglycaemic action of adrenaline

There is an important degree of competitive inhibition between some, at least, of the actions of the different ergot alkaloids Rothlin and Cerletti (1950a) showed that the vasoconstrictor action of ergotamine can be antagonized by pre-treatment with the dihydrogenated ergot alkaloids Another example of competitive action is the use of dihydrogenated ergot alkaloids to overcome the uterine stimulation induced by the natural ergot alkaloids

## Clinical Studies with the Dihydrogenated Ergot Alkaloids

Following the pharmacological studies of Rothlin, Bluntschli and Goetz (1947) described the hypotensive action of the dihydrogenated ergot alkaloids in man, and in 1949 Kappert published a monograph describing clinical studies appropriate to sympatholytic agents. Much investigation followed concerning the action of these drugs in man and the possibility of their therapeutic use.

## Oral and Parenteral Dosage

It is clear that almost all observers have recorded falls of blood pressure following the intravenous administration of Hydergine [22, 88, 104, 110, 112, 192, 236, 261] or of dihydroergocornine [25, 88, 110, 113, 239]. The doses of Hydergine used ranged from 0.25 to 0.6 mg. The extent of the blood pressure falls after intravenous administration varied from case

be associated with collapse. Presumably the difference is one of cardiac output.

Inhibition of the blood pressure rise in response to the cold pressor test of Hines and Brown (1932) has been reported by Kappert (1949), Moister, Stanton and Freis (1949), Kappert et al. (1952) and Freis et

[illegible]

ing the Valsalva experiment were prevented or decreased by hydrogenated ergot alkaloids [76, 133, 164].

Lasch (1952) considers that a salt-poor diet (3 to 4 G. urinary output of NaCl in 24 hours) also enhances the depressor action of Hydergine.

*Cerebral circulation.* — Hafkenschiel et al. (1950) reported there was a significant decrease in the cerebral vascular resistance after giving dihydroergocornine (0.3 to 0.5 mg. intramuscularly). The cerebral blood flow, the cerebral arteriovenous oxygen difference and the cerebral oxygen metabolism were unchanged at a time when the mean arterial blood pressure was decreased.

*Retinal circulation.* — Gibbs (1952) observed a distinctive relaxation of the spasm of retinal arterioles. The arterioles dilated within 10 minutes of making the injection and in nine cases the effect lasted up to twelve hours.

*Renal circulation.* — According to Freis et al. (1949b) the renal blood flow increases initially but later returns to control levels. Deutsch

[illegible]

widening of the renal arterioles.

[illegible] ...oids [illegible] ... al. [illegible] ..., with a somewhat smaller decrease in the glomerular filtration rate. This persisted for at least 60 minutes after the intramuscular administration of 0.5 mg. of dihydroergocornine. They consider that there is renal vasoconstriction. They make the suggestion that the renal vascular bed has constricted, acting as a circulatory regulator in order to divert blood to the brain.

The general impression is that sufficiently large doses decrease the renal plasma flow but that no lasting reduction of blood flow results from the continued administration of moderate doses.

*Splanchnic circulation.* — Grayson and Swan (1950) made the interesting observation that dihydroergocornine (0.5 mg. intravenously) caused a fall in the systolic blood pressure, a rise in skin temperature and a fall in the temperature of the bowel which was exposed by a

Zickgraf (1949) finds that in health, essential hypertension, contracted kidney and angina pectoris the administration of Hydergine (0.3 mg. intramuscularly) causes a decrease in the systolic and diastolic blood pressures, decrease in the pulse pressure, decrease in the pulse rate, decrease in the stroke and minute volume, and, surprisingly enough, an increase in the peripheral resistance as calculated. An increase of peripheral resistance has been reported also by Blumberger (1950) and Völker and Kaczmarek (1950). Kappert (1949), however, considers that the peripheral resistance is reduced.

The fall of blood pressure after dihydrogenated ergot alkaloids may be modified in several ways. Goetz (1951) found that after a Smithwick sympathectomy the blood pressure fall from dihydroergocornine is diminished or absent, although the heart rate decreases.

The effect of increasing sympathetic tone is demonstrated in an experiment described by Kappert, Baumgartner and Rupp (1948) who showed that, when the blood pressure was raised in hypertensive patients by tight ligature of both legs just below the groin, the subsequent administration of 0.3 mg. of Hydergine led to an immediate and strong fall of blood pressure. The fall of blood pressure was greater than that which occurs after intravenous Hydergine when ligatures have not been previously applied.

Postural hypotension has been reported following the administration of hydrogenated ergot alkaloids [30, 81, 84, 87, 131, 184]. The postural hypotension has been observed in normotensives as well as hypertensives. Either the inhibition of central vasoconstriction or the peripheral sympatholytic action could explain the postural hypotension. It seems likely that both factors operate, but mainly the central action.

There is other evidence that the homeostatic mechanisms are inhibited. Freis et al. (1951) found that, following the administration of dihydroergocornine, the effect of venesection upon the blood pressure was far greater than normal. Removal of as little as 200 ml. caused a decrease of the blood pressure.

Freis et al. (1951) showed that, following the administration of dihydrogenated ergot alkaloids to normotensive or hypertensive patients, there developed a predisposition to falls of blood pressure and to circulatory collapse. When the limbs were congested with a tourniquet which raised the venous pressure, the excess of blood pooled in the limbs was of the order of 520 ml. The falls of blood pressure during this venous congestion were very much greater if the congestion were applied during the action of dihydroergocornine (0.5 mg. intravenously). It is of interest that the experiment was made with the subjects in the horizontal posture and that collapse was reported at pressures such as 98/66, 88/70, 90/35, 108/56, 85/62, 80/60, 90/80, 85/75, and 68/40. Such pressures (except for the last one or two), if induced in the horizontal posture by methonium salts without congestion would not

however, could be relieved by local application of 0.25 per cent neo-synephrine. Nausea occurred in 7 out of 40 patients and in three of these there was vomiting. There was no change in visual accommodation.

Others have reported that emesis is an occasional side effect. There may be nausea and anorexia [132]. Emesis is probably due to stimulation of the emetic centre. The action seems to occur in hypertensive as well as normotensive patients [30, 67]. Kappert, Baumgartner and Rupp (1948) also refer to occasional diarrhoea. They recommend that increase in the dose of Hydergine should be gradual.

Dupuy, Signorelli and Attyah (1952) studied 25 patients for 18 to 36 months. Their average maximum daily dose was 7.5 mg. by tablets or 5 6 mg. in liquid form. Hypotensive effects were infrequent, small in degree and of short duration Four of their patients had mild nausea, two had dizziness and three were drowsy. Although no alarming reactions occurred, several patients asked for the drug to be discontinued They point out, however, that with large enough doses the blood pressure falls

Gibbs (1952) did not think the side affects were severe. Among 17 patients he noticed nasal congestion in 12, nausea in 3, vomiting in 1, and drowsiness in 5. The doses he used produced small falls of blood pressure in 12 out of 17 cases A comparison was made with placebos. Bechgaard and Paulsen (1953) mention headache as a side effect.

Tandowsky (1950) encountered toxic reactions in 30 out of 47 patients with intravenous dihydroergocornine but they were only alarming in two. Nasal stuffiness was encountered in 21 patients; dryness of the mouth in 4 patients, nausea, faintness, chills and feelings of warmth in 3 patients each; vomiting, dyspnoea, syncope, dizziness, weakness, sweating and impaired vision in 2 patients each; tingling, lethargy, cold and clammy feelings, flushing, delayed circulation, headache, sense of fullness in the head and tenderness of the breast in one patient each The oral doses responsible ranged from 0.5 to 15 mg. daily

## Treatment of Hypertension by Dihydrogenated Ergot Alkaloids

In assessing reports on the use of dihydrogenated ergot alkaloids in the treatment of high blood pressure one must recollect that many of the reports were written at a time most of the drugs upon which reliance is now placed were unavailable; and there was every reason to acclaim even minor degrees of clinical improvement. Consequently, many of the results which were good for the period of time in which the papers were written are to be regarded as poor results at the present time Moderately favourable results were reported by Kappert (1949), Sarre (1949), Gast and Hueber (1950) and Hadorn (1952). Slightly better results were obtained by the hydrogenated ergot alkaloids than

colostomy. Local infiltration of the bowel with saline produced a drop of temperature; local infiltration of the bowel with Hydergine dissolved in saline produced a drop followed by substantial rise in temperature. Even in experiments in which there was no fall of blood pressure there appeared to be constriction in this exposed splanchnic region. The direct effect of dihydroergocornine applied to the bowel is apparently vasodilatation, the observed effect of its intravenous injection is vasoconstriction. The authors conclude that the vasoconstriction is due to a nervous reflex which is strong enough to overcome the peripheral (presumably sympatholytic) action. Freis et al. (1949b) studied the estimated hepatic portal blood flow, which they found to be variable.

*Limb circulation.* — Bluntschli and Goetz (1948) showed that dihydroergocornine induces vasodilatation in a normally innervated limb but it does not produce vasoconstriction in a sympathectomized limb. Hence, in the doses used, and in the human limbs studied, dihydroergocornine had no obvious direct vasoconstrictor action. In animal experiments dihydroergocornine, dihydroergocristine, dihydroergokryptine and the mixture, Hydergine, stimulate the smooth muscle of blood vessels directly, leading to mild vasoconstriction in denervated vessels. The experiments of Bluntschli and Goetz (1948) show that this action is not important in man in the doses ordinarily used.

In man an intra-arterial injection of hydrogenated alkaloids gives rise to local vasodilatation [131]. This vasodilatation is actually greater if adrenaline and the ergot alkaloids are injected at the same time. A possible inference is that the adrenergic vasodilator mechanisms are not inhibited by the dihydrogenated alkaloids. The vasoconstrictive action of cold in vasospastic conditions, such as Raynaud's disorder, is overcome by the dihydrogenated alkaloids. A medical colleague who had a severe Raynaud's condition had more complete relief from oral Hydergine than from any other drug The improvement while on Hydergine lasted over two years.

## Toxic or Side Effects of Dihydrogenated Ergot Alkaloids

It is generally agreed that, in the doses ordinarily used, such toxic or side effects as occur with the use of dihydrogenated ergot alkaloids disappear shortly after stopping the drug or reducing the dose. There appears, for example, to be no danger of gangrene, as the direct stimulating action on the smooth muscle of blood vessels is of but subsidiary importance, being overshadowed by actions which dilate blood vessels.

It is stated by Gast and Heuber (1950) that the drug is comparatively free from side effects, even with rather high oral doses, such as 1 mg. of Hydergine five times daily, together with intramuscular injections of as much as 1 mg. thrice daily. Such high doses in our experience usually give rise to congestive nasal obstruction. Freis, Stanton and Wilkins (1948) observed nasal congestion in almost every case which,

however, could be relieved by local application of 0.25 per cent neo-synephrine. Nausea occurred in 7 out of 40 patients and in three of these there was vomiting. There was no change in visual accommodation.

Others have reported that emesis is an occasional side effect. There may be nausea and anorexia [132]. Emesis is probably due to stimulation of the emetic centre. The action seems to occur in hypertensive as well as normotensive patients [30, 87]. Kappert, Baumgartner and Rupp (1948) also refer to occasional diarrhoea. They recommend that increase in the dose of Hydergine should be gradual.

Dupuy, Signorelli and A[illegible] (1952) studied 25 patients for 18 to 36 months. Their average n[illegible] or 5.6 mg. in liquid form. [illegible] in degree and of short duration. Four of their patients had mild nausea, two had dizziness and three were drowsy. Although no alarming reactions occurred, several patients asked for the drug to be discontinued. They point out, however, that with large enough doses the blood pressure falls.

Gibbs (1952) did not think the side affects were severe. Among 17 patients he noticed nasal congestion in 12, nausea in 3, vomiting in 1, and drowsiness in 5 The doses he used produced small falls of blood pressure in 12 out of 17 cases. A comparison was made with placebos. Bechgaard and Paulsen (1953) mention headache as a side effect.

Tandowsky (1950) encountered toxic reactions in 30 out of 47 patients with intravenous dihydroergocornine but they were only alarming in two. Nasal stuffiness was encountered in 21 patients; dryness of the mouth in 4 patients, nausea, faintness, chills and feelings of warmth in 3 patients each; vomiting, dyspnoea, syncope, dizziness, weakness, sweating and impaired vision in 2 patients each; tingling, lethargy, cold and clammy feelings, flushing, delayed circulation, headache, sense of fullness in the head and tenderness of the breast in one patient each The oral doses responsible ranged from 0.5 to 15 mg. daily

## Treatment of Hypertension by Dihydrogenated Ergot Alkaloids

*In assessing reports on the* use of dihydrogenated ergot alkaloids in the treatment of high blood pressure one must [illegible]

[illegible] to be regarded as poor results at the present time Moderately favourable results were reported by Kappert (1949), Sarre (1949), Gast and Hueber (1950) and Hadorn (1952). Slightly better results were obtained by the hydrogenated ergot alkaloids than

by placebos by Kühns and Vogel (1951) and Gibbs (1952). Indefinite results were described by Prusik (1948). Subjective clinical improvement without much blood pressure fall was described by Zickgraf (1949) and Tandowsky (1954). Symptomatic relief from dizziness and headache was described by Nuzum (1950) and Tandowsky (1954).

There were few reports of the objective clinical improvements which are familiar now with more effective hypotensive agents; but the improvements, when they occurred, were of the same kind. Hager (1951), however, noted in some cases a decrease of papilloedema and retinal exudate and Gibbs (1952) recorded a decrease in papilloedema in one case. Tourniaire, Guyot and Moreteau (1952) described the regression, or at least partial diminution, in the amount of papilloedema in 6 out of 19 patients. It is of interest that the authors used subcutaneous or intramuscular injections in 6 cases, oral administration in 10 cases and combined oral and parenteral administration in 12 cases, While there were 6 patients whose ocular fundi showed improvement. there were 9 who showed a deterioration. Gibbs (1952) found no improvement in the electrocardiogram. Wilbrandt (1953) followed a number of malignant hypertension cases for 1 year and found 60 per cent survived, which is better than the survival in the Keith-Wagener series of cases.

Decrease in angina was noted by Schimert and Zickgraf (1949) and Echave (1952) but not necessarily in relationship to the occurrence of a blood pressure fall. This is of particular interest because the decrease in the heart rate and, in certain cases, in the cardiac output might explain a decrease in the cardiac overload and consequently improvement in the angina, even in the absence of a fall of blood pressure.

In recent times Tandowsky has studied the hydrogenated ergot alkaloids. He points out that in hospital these may be used by injection to produce effective blood pressure falls, but the short duration of the effect makes their use unpractical for the control of ambulatory patients. A carefully controlled investigation by McGregor, Zion and Bothwell (1954) indicated practically no therapeutic difference between orally administered Hydergine and a placebo. The incidence of side effects was higher with the Hydergine than with the placebo.

In a recent report by Wilbrandt (1953) 200 ambulant hypertensives were treated. In mild cases with grade 1 and grade 2 fundi, 59 per cent had lowering of the blood pressure and 80 per cent had an improvement of subjective symptoms. In severe cases with grade 3 and 4 fundi lowering of the blood pressure took place in 31 per cent and there was 52 per cent of subjective improvement. Most of the blood pressure falls reported in this paper were comparatively small.

## Comment on the Dihydrogenated Ergot Alkaloids

The dihydrogenated ergot alkaloids are of great pharmacological

... in the treatment of hypertension

these substances are ...
given parenterally. ...
in combination with ganglion blocking drugs; but observed no further fall of blood pressure. Hydergine (0.25 to 0.5 mg. sublingually or swallowed) finds useful employment in reducing the tachycardia which occurs as an unusual complication of ganglionic blockade.

## THIOCYANATES

Claude Bernard, ... 1856, showed that thiocyanates caused direct depre... muscle in the frog, ... appears to have come first from Pauli (1903) who described the sedative and hypotensive actions He obtained relief of subjective symptoms in patients with hypertension. Le Roy (1909) also gave an account of the hypotensive action.

There has been much confusion regarding the hypotensive action of thiocyanates This arises because the falls of blood pressure with non-toxic doses are often within the range of the normal variation of the blood pressure and because thiocyanates have two or more pharmacological actions which might aid blood pressure reduction. These actions are stated to be:

1. A mild sedative action.
2. A decrease in the activity of the thyroid gland.
3. Probably a decrease in the cardiac output.
4. Perhaps direct inhibition of smooth muscle.

### Experimental Pharmacology

Bacq et al. (1948, 1949) found a decrease in the cardiac output of dogs given sodium thiocyanate intravenously, but there was no reduction in the blood pressure. This effect was found to be largely dependent upon the integrity of the vagus nerves. Bacq attributed the effect on cardiac output to an increase in the sensitivity of the heart to vagal tone. Goodman and Gilman (1955) also state that large doses in experimental animals do not decrease the blood pressure

An effect ...
perimental a...
the potassium thiocyanate inhibits the uptake of iodine by the rat thyroid

It is also of interest that Goldstein and Rieders (1951) found that the administration of thiocyanate in the dog and in man led to the liberation of significant amounts of cyanide. The question arises whether alterations of tissue respiration occur as a result of this. An

inhibition of the enzyme carbonic anhydrase was described by Davenport (1940). Davenport thinks this action may explain the reduced secretion of acid in the stomachs of dogs treated with thiocyanate and it has been suggested that it sometimes leads to diuresis. Hoffmeister

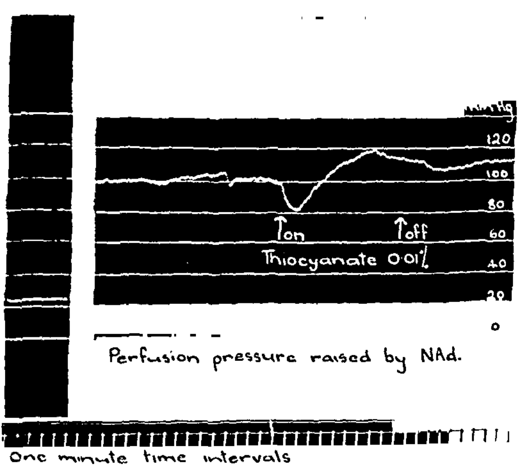



Fig XVI 4

the perfusion fluid The thiocyanate ion causes a fall followed by a rise in the perfusion pressure. (Field, L W., and Laverty, R personal communication).

and Kruck (1954) also draw attention to the effect of potassium thiocyanate on carbonic anhydrase and think increased excretion of sodium may explain the hypotensive action. Field and Laverty (1956) found no evidence of significant vasodilatation in perfused rat blood vessels, even when the vessels were contracted by the addition of vasoconstrictor agents to the perfusion fluid (Fig. XVI 4). On the contrary, vasoconstriction was the more usual response when thiocyanate was added to the perfusion fluid.

## Clinical Studies with Thiocyanates

*Action on the blood pressure.* — In general, blood pressure falls with sub-toxic doses of potassium thiocyanate are of moderate extent requiring in many instances control experiments with placebos for their confident recognition. The falls, however, may be considerable. Particularly is this the case when toxic doses have been given. Alstad (1948) described a patient who took excessive doses and developed a toxic psychosis, the blood pressure fell from 190/110 to 88/52 and rose again as the thiocyanate was eliminated. Domzalski et al. (1953) referred to the blood pressure changes in two patients with thiocyanate intoxication. In one instance the systolic blood pressure fell from over 300 to 150 mm. Hg and in another from 270/130 to 140/80. Healy (1931) described a fatal case of poisoning on doses of about 1 gm. daily, with a blood pressure fall from 205/100 to 110/70.

In conventional doses, with blood thiocyanate concentrations between 8 and 12 mg. per 100 ml., the blood pressure falls are seldom impressive There seems, however, to be little doubt that, in general, the falls of blood pressure exceed those which occur during administration of placebos.

Particular interest attaches to careful observations by Alstad (1949) who showed that, when a comparison was made with placebos, the administration of thiocyanates reduced both the basal and the supplemental (casual — basal) pressures; but placebos reduced only the supplemental pressures Fig. XVI 5.

*Other clinical observations.* — Some effect upon the adrenal cortex

certain if these changes influence the blood pressure level.

It is possible that these histological changes should be considered in relationship to the observations of Pines and Perera (1952) that a small but highly significant sodium diuresis is induced in normotensives and hypertensives by the administration of thiocyanates. These authors considered the possibility that sodium depletion might be a factor in the depressor action of thiocyanates. An alternative explanation may be found in the inhibition of carbonic anhydrase, referred to earlier.

The effect on the thyroid gland of the thiocyanate ion has been demonstrated in man [21]. The thiocyanate ion reduces the iodide con-

ead to discharge of

1939) and Richards

... rate could be reduced in hypertensive patients by the administration of thiocyanates and Richards et al. (1949) described the occurrence of thyroid enlargements. Beamish et al. (1954) noted that the effect on the thyroid gland

could be largely prevented by the administration of potassium iodide, without interfering with the hypotensive action.

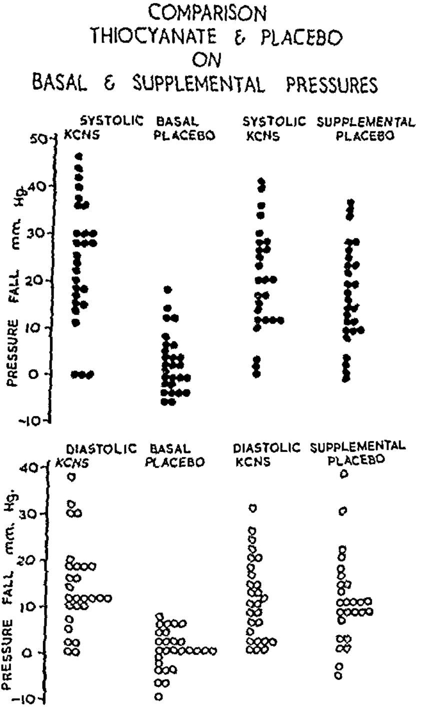



Fig. XVI 5

Reduction of blood pressure in thirty-two patients treated with potassium thiocyanate and with a placebo (Diagram based on figures taken from Table I, Alstad, K. S, *Brit. Heart J*, *11* : 240, 1949).

The thiocyanate ion diffuses rapidly but most of it has been shown to remain in the extracellular phase [147, 212].

## Treatment of Hypertension with Thiocyanates

*Control of dosage.* — It is quite generally agreed that a limit must be placed on the amount of thiocyanate administered, which is determined by estimations of the blood thiocyanate, and this must not be allowed to rise above 12 mg. per 100 ml. (expressed as thiocyanate ion). An ordinary initial dose is 0.1 gm. of sodium or potassium thiocyanate thrice daily and this [illegible] to 0.2 gm. three or four times daily, provided always tha[illegible]
cent. Barker [illegible]

In well controlled studies on hypertensive patients it seems that thiocyanate administration causes falls of blood pressure which are somewhat in excess of the effects obtained by placebos [5, 16, 17, 19, 21, 201, 206, 245]. There have also been several reports of moderate blood pressure falls and symptomatic benefits [1, 20, 61, 267].

Nichols (1925) and Smith and Rudolf (1929) often used doses of 1 gm. daily of sodium thiocyanate and reported blood pressure falls between 20 and 80 mm. systolic. Toxic effects occurred frequently on these doses, for at this time control by the blood thiocyanate had not been introduced.

Several writers have laid great stress on the relief of severe hypertensive headaches by thiocyanates [3, 4, 44, 69, 150, 227]. Some find little relationship between symptomatic improvement and the extent of the fall in blood pressure

## Toxic Effects

The urinary excretion of the thiocyanate ion is variable, so that determinations of the blood thiocyanate levels are necessary to determine the appropriate dosage level. When this is done moderate or large series of patients may be treated with comparatively few toxic reactions; but toxicity is not to be avoided altogether by this precaution [63].

Goldring and Chasis (1932a, b), Wald, Landberg and Barker (1939) Hines (1952) and Domzalski et al. (1953) gave accounts of the toxic reactions encountered with thiocyanate administration. Probably psychotic delirium is one of the most dangerous. Domzalski et al. (1953) gave references to the literature: a total of 46 examples of thiocyanate psychosis had been reported with deaths in 17.

The early signs of the psychosis are clouding of consciousness, apathy, loss of memory, restlessness, confusion, somnolence, hallucinations and disorientation. Most writers are impressed by the seriousness of such psychotic reactions. Other toxic effects are skin rashes, anaemia, agranulocytosis, thrombocytopenic purpura, enlargements of the thyroid gland and osteoporosis. The rashes encountered include a

maculopapular rash with itching, an exfoliative dermatitis and oedema of the face. Mild gastrointestinal symptoms are also encountered after several years of thiocyanate treatment. Wald et al. (1939) had several patients who developed anaemia and emaciation. They noted similar findings in experimental animals.

### Comment

There is little doubt that blood pressure reduction and symptomatic relief may be obtained in some patients by thiocyanate treatment. The degree of blood pressure reduction and of objective clinical improvement are, in the author's view, insufficient to justify the continued use of this substance.

## OTHER DRUGS

### Sodium Nitroprusside

Early observations on sodium nitroprusside, $Na_2[Fe(CN)_5(NO)]2H_2O$, were made by Johnson (1929). Attention has been directed recently to its actions in man by Page and his co-workers [184, 185]. When given orally to animals or to hypertensive patients its actions are indistinguishable from those of thiocyanates both in regard to its effect on the blood pressure and in respect of toxic side effects. Apparently the substance is converted to thiocyanate and the concentration of thiocyanate in the serum should not be allowed to rise above 12 mg. per 100 ml. The oral dose is usually 30 to 60 mg. four times daily. In 9 out of 16 patients on oral doses, Page et al. (1955) obtained falls of blood pressure of 20/15 mm. Hg or more.

When sodium nitroprusside is administered by intravenous injection there appears to be a strong, direct effect of the drug on blood vessels leading to impressive falls of blood pressure (Field and Laverty, 1956) (Fig. XVI 6). Page et al. (1955), have administered nitroprusside to patients by continuous intravenous injection, at rates of 25 to 380 micrograms per minute. The falls of blood pressure were prompt and the extent of the fall seemed to be a question of dosage. Blood pressure falls were recorded of up to 144/120. A decrease in blood pressure was also observed in 2 normotensives. The administration of hexamethonium enhanced the blood pressure fall from nitroprusside. No deleterious effect was noted by Page in rats receiving repeated intravenous injections. The effective dose in man is 400—800 mg daily. The renal blood flow was not much changed.

### Nitrites and Organic Nitrates

Nitrites and organic nitrates will reduce the blood pressure when given in adequate doses, the organic nitrates being the more active agents. Thus, a suitable dose of glyceryl trinitrate is 0.5 mg. as con-

trasted with sodium nitrite 40 mg. The suggestion has been made that organic nitrates act by being converted to nitrites. This explanation is not easy to accept unless one assumes that the chemical change occurs intracellularly, or close to the site of action; for otherwise the much greater pharmacological activity of organic nitrates would be difficult to explain. Alternatively, organic nitrates may act directly on the smooth muscle of blood vessels without undergoing any chemical transformation.

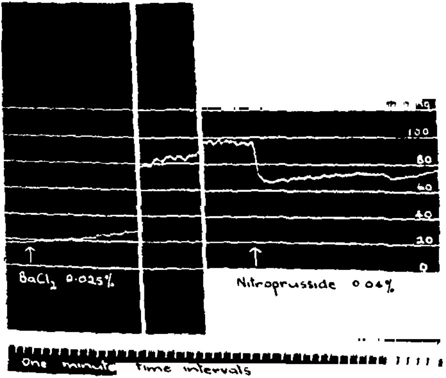



Fig. XVI 6

The effect of sodium nitroprusside, 0 04 per cent, has been tested on the blood vessels of the pithed hindquarters of rats perfused at constant rate with Krebs and Henseleit solution. The perfusion pressure has been raised by the addition of barium chloride to the perfusion fluid The nitroprusside ion causes a prolonged fall in perfusion pressure. (Field, L W, and Laverty, R, personal communication).

The blood vessels chiefly affected are postarteriolar, namely, capillaries and venules (Wilkins et al., 1937). This leads to excessive pooling of blood in dependent capillaries and veins, especially in the vertical posture, hence, the occurrence of postural hypotension. The circulatory effect of the pooling is similar to that induced by a considerable reduction of blood volume, and a decrease in the cardiac output and

orthostatic collapse may occur. In hypertension the blood pressure falls after nitrite administration are not readily controlled. Orthostatic collapse is not infrequent after effective hypotensive doses of nitrites or of organic nitrates but usually this symptom can be relieved by lying flat (Weiss et al., 1937; Leuth and Hanks, 1938). The arteriolar peripheral resistance may be increased by nitrite, probably as the result of regulatory reflexes (Wilkins et al., 1937). A degree of drug toleration develops with repeated administration.

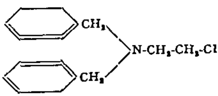
Probably the main reason why nitrites and organic nitrates have had no success in the treatment of hypertension is that the blood pressure reduction is due mainly to diminished cardiac output, hence a fall in blood pressure is more likely to be associated with orthostatic collapse. We attempted to use Peritrate as an ancillary hypotensive agent in combination with pentolinium, but the results obtained did not seem to justify the complication of adding an additional drug to the régime.

## Sulphydryl Compounds

Schroeder (1951, 1953) considers that substances containing a sulphydryl group on the end of a two or three carbon chain are specifically anti-hypertensive. He mentions 2—3 dimercaptopropanol (BAL) as being pressor in normotensives and depressor in hypertensives. He says, "Sulphydryl compounds are true anti-hypertensive agents, the only substances which raise normal blood pressure and lower high blood pressure". Certain sulphydryl compounds inhibit the action of Pherentasin which Schroeder considers to be a specific substance existing in hypertensive blood but not in normotensive blood. Schroeder (1953) links with his remarks on sulphydryl compounds the idea that an extraneous metal may substitute for an essential one on the protein of an enzyme, so inactivating enzymatic processes concerned with oxidizing amines, especially Pherentasin. Perry (1953) finds the sulphydryl content of urine markedly diminished in hypertensive patients.

## Dibenamine (N,N-dibenzyl-$\beta$-chloroethylamine)

Dibenamine, a chemical relative of the nitrogen mustards, is one of a class of adrenergic blocking agents described by Nickerson and Goodman (1947).




*Dibenamine.*

It is far too toxic a substance to have any lasting clinical value but the study of its pharmacology is of great theoretical interest.

Moderate doses of dibenamine have comparatively little action on the blood pressure in experimental animals or in (normal) human subjects[108, 114]. In hypertension, however, there may be considerable blood pressure falls[24, 108, 109, 168]. The average of the maximal pressure falls obtained by Wunsch et al. (1950) were 50/38 with doses of 2 to 10 mg. per kg. in 14 patients. The fall of blood pressure takes as long as 2½ hours to reach its trough and lasts 24 hours as an average[274], but it may on occasion last as long as 5 or 6 days[108, 274]. Most workers who have administered dibenamine in man have used 5 mg. per kg. of body weight by intravenous injection[228].

[illegible] adrenolytic and mildly sympatholytic; it [illegible]

[illegible] the inhibitory responses of smooth muscle to adrenaline are not [illegible]ed. The pressor action of angiotonin and pituitrin is not prevented by the administration of dibenamine[59, 278]

In dogs the adrenergic block prevents the ventricular tachycardia and fibrillation which may be produced by toxic doses of adrenaline. Other sympatholytic effects are the occurrence of miosis[274] and in cats, relaxation of the nictitating membrane In man the response of the blood pressure to a small dose of adrenaline is either diminished or reversed[114] In animals vasoconstriction, which ordinarily results when the splanchnic nerves are stimulated, may be replaced by vasodilatation after dibenamine (Nickerson and Nomaguchi, 1953).

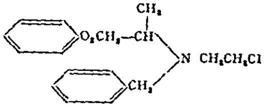
The cardiac acceleration induced by adrenaline is not prevented by dibenamine. Postural hypotension is usual[108, 114, 223, 274] and other effects due to sympathetic inhibition have been reported in man, such as decrease in the reaction to the cold pressor test[274]. The carotid sinus pressor reflexes are also inhibited in dogs[157] Wunsch et al. (1950) described clinical improvement in a case of hypertensive encephalopathy.

*Toxic effects* — Dibenamine is a highly irritant substance. In man it has caused serious local irritation when injected subcutaneously or intramuscularly Local thrombosis has followed its intravenous administration[228] Nausea and vomiting are likely to follow administration by mouth[108, 121, 181, 274]. We made a few investigations with dibenamine administered orally. In one patient haematemesis occurred, in another there was considerable vomiting. We regarded the substance as quite unsuitable for oral administration. Psychical upsets have followed the administration of dibenamine. These do not appear to be associated with the blood pressure falls. Spühler (1948) and Wunsch et

al. (1950) described mental confusion and epileptiform convulsions.

**Dibenzyline** (688A or N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride)

The remarkable adrenolytic action of dibenamine led to a study of some of its chemical relatives. Of these dibenzyline proved to possess the most satisfactory therapeutic ratio [17].



Dibenzyline (688A)

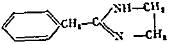
The extent of the blood pressure fall in hypertension is related to the dose used. For the most part the blood pressure falls obtained with doses such as 50 to 200 mg. by mouth have been moderate in degree.

Woodward, Hoobler and Nickerson (1952) gave dibenzyline intravenously to hypertensive patients and observed an increase in the blood flow through the foot. There was also a mean fall in blood pressure of 38/25 which occurred ½ to 1 hour after the infusion and persisted for 1 to 2 hours.

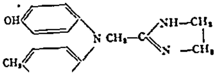
Allen et al. (1951) gave up to 1 mg. per kg. body weight intravenously in 13 hypertensive patients and obtained falls of blood pressure of between 24/35 and 100/70. Moser et al. (1952) using doses of 40 to 200 mg. t.d.s. orally obtained falls which ranged from 15/15 to 60/19. There is general agreement that postural hypotension develops after the administration of dibenzyline [2, 17, 169, 272]. Drug toleration develops to the hypotensive action [86, 169] and the pulse rate is increased [272]. As with dibenamine, there is a decrease in the response to the cold pressor test [169] and diminished reaction to the Valsalva pressor overshoot [169]. Breath holding for 20 seconds no longer causes a blood pressure increase [169]. A decrease in the pressor response to adrenaline, sometimes with reversal of the response, was reported by Bakke and Williams (1953). Allen et al. (1951) described effective blood pressure reduction in a patient with phaeochromocytoma.

Moyer and Handley (1952), who studied the renal function in dogs, found a decrease in the renal vascular resistance and usually a slight increase in the renal blood flow The glomerular filtration rate was not altered significantly. The general impression has been that as the sole form of medication in essential hypertension dibenzyline has limited usefulness [2, 17, 86, 109, 169]. Our own observations are consistent with this general impression.

### Tolazoline (Priscoline) and Phentolamine (Regitine)



Tolazoline (Priscoline)



Phentolamine (Regitine)

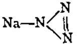
[illegible] vascular disease but do not regularly reduce the [illegible]

because of the increase in cardiac output, which is probably due, at least partly, to a direct action on the heart. Indeed, tolazoline sometimes raises the blood pressure alarmingly. Tachycardia and cardiac arrhythmias may [illegible] ment may be p[illegible] diarrhoea [37, 173]. [illegible] loss of therapeutic activity [40, 173]. The usual doses by mouth are: Priscoline 25 mg. after meals, increasing gradually if needed to 100 mg.; Regitine 50 to 100 mg. several times daily. In the diagnosis of phaeochromocytoma 5 mg of Regitine is given intramuscularly or intravenously.

#### Andromedotoxin

This substance is an active principle from Rhododendron maximum. It is a powerful but toxic hypotensive agent. Moran et al. (1954a, b) found that the hypotensive action was due to a stimulation of the carotid bodies and/or sinuses, leading to vasodilatation. We were impressed by its toxicity in a few preliminary studies in animals and made no clinical trials

#### Sodium Azide

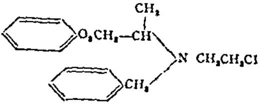


Sodium azide administered sublingually induces a very prompt fall of blood pressure in some hypertensive patients. Its circulatory effects

al. (1950) described mental confusion and epileptiform convulsions.

**Dibenzyline** (688A or N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride)

The remarkable adrenolytic action of dibenamine led to a study of some of its chemical relatives. Of these dibenzyline proved to possess the most satisfactory therapeutic ratio [17].




Dibenzyline (688A)

The extent of the blood pressure fall in hypertension is related to the dose used. For the most part the blood pressure falls obtained with doses such as 50 to 200 mg. by mouth have been moderate in degree.

Woodward, Hoobler and Nickerson (1952) gave dibenzyline intravenously to hypertensive patients and observed an increase in the blood flow through the foot. There was also a mean fall in blood pressure of 38/25 which occurred ½ to 1 hour after the infusion and persisted for 1 to 2 hours.

Allen et al. (1951) gave up to 1 mg. per kg. body weight intravenously in 13 hypertensive patients and obtained falls of blood pressure of between 24/35 and 100/70. Moser et al. (1952) using doses of 40 to 200 mg. t.d.s. orally obtained falls which ranged from 15/15 to 60/19. There is general agreement that postural hypotension develops after the administration of dibenzyline [2, 17, 169, 272]. Drug toleration develops to the hypotensive action [86, 169] and the pulse rate is increased [272]. As with dibenamine, there is a decrease in the response to the cold pressor test [169] and diminished reaction to the Valsalva pressor overshoot [169]. Breath holding for 20 seconds no longer causes a blood pressure increase [169]. A decrease in the pressor response to adrenaline, sometimes with reversal of the response, was reported by Bakke and Williams (1953). Allen et al. (1951) described effective blood pressure reduction in a patient with phaeochromocytoma.

Moyer and Handley (1952), who studied the renal function in dogs, found a decrease in the renal vascular resistance and usually a slight increase in the renal blood flow. The glomerular filtration rate was not altered significantly. The general impression has been that as the sole form of medication in essential hypertension dibenzyline has limited usefulness [2, 17, 86, 109, 169]. Our own observations are consistent with this general impression.

clinical studies on pheochromocytoma and essential hypertension. Trans Ass. Amer. Phys., 64: 109, 1951.

3 ALLEN E. V., BARKER N. W., HINES, E. A., Jr., KVALE, W. F., SHICK, R. M., GIFFORD, R. W., and ESTES, J. E., Jr. Medical treatment of essential hypertension. Proc. Mayo Clin., 29: 459, 1954.

4 ALSTAD, K. S. Effect of thiocyanate on basal blood pressure. Brit. med. J., 1: 250, 1948.

5 ALSTAD, K. S. The effects of thiocyanate on basal and supplemental blood pressures. Brit. Heart J., 11: 249, 1949.

6 AMANN, A., and SCHAEFER, H. Ueber sensible Impulse im Herznerven. Pflugers Arch. ges. Physiol., 246: 757, 1943.

7 ASHE, J. R., Jr., and THOMAS, W. L. Hexamethonium chloride and apresoline in toxemia of pregnancy — A preliminary report. Obstet. Gynec., [illegible]

8 ASSA[illegible]

9 ASS[illegible] Hemodynamic effects of a [illegible] line) in hypertensive complications of pregnancy. Amer. J. Med., 14: 491, 1953.

10 ASSALI, N. S., BRUST, A. A., GARBER, S. T., and FERRIS, E. B. Comparative study of the effects of tetraethylammonium chloride and veratrum viride on blood pressure in normal and toxemic pregnancy. J. clin. Invest., 29: 290, 1950

11 ASSALI, N. S., and SUYEMOTO, R. The place of the hydrazinophthalazine and thiophanium compounds in the management of hypertensive complications of pregnancy. Amer. J. Obstet. Gynec., 64: 1021, 1952.

12 BACQ, Z. M. Sensibilisation au potassium par la vératrine. C. R. Soc. Biol. (Paris), 130: 1369, 1939a

13 BACQ, Z. M. Ions et corps vératrinique. Arch. int. Pharmacodyn., 63: 59, 1939b

14 BACQ, Z. M., CHARLIER, R., PHILIPPOT, E., and FISCHER, P. Réduction par le sulfocyanure de sodium du débit cardiaque du chien. Arch. int. Pharmacodyn., 77: 347, 1948

15 BACQ, Z. M., CHARLIER, R., PHILIPPOT, E., and FISCHER, P. Action of sodium thiocyanate on cardiac output. Brit. J. Pharmacol., 4: 162, 1949

16 BAKER, P. DE L. Therapeutic uses of veratrum viride. London Lancet, 1: 362, 1860

17 BAKKE, J. L., and WILLIAMS, R. H. Treatment of essential hypertension with β-alkylamines, especially dibenzyline. Amer. J. Med., 14: 141, 1953

18 BARKER, M. H. The blood cyanates in the treatment of hypertension. J. Amer. med. Ass., 106: 762, 1936

19 BARROW, J. G., and SIKES, C. R. The use of purified veratrum alkaloids in the treatment of essential hypertension. Amer. Heart J., 41: 742, 1951

20 BEAMISH, R. E., and ADAMSON, J. D. The treatment of essential hypertension with sodium thiocyanate. Canad. med. Ass. J., 53: 236, 1945

21 BEAMISH, R. E., PERRY, W. F., and STORRIE, V. M. Observations on thyroid function in hypertensive patients treated with potassium thiocyanate. Amer. Heart J., 48: 433, 1954

22 BECHGAARD, P., and PAULSEN, L. Dihydrogenated ergot alkaloids (hyder-

in animals and in man have been studied by Black, Zweifach and Speer (1954). It has the effect of inhibiting many enzyme systems and is generally regarded as potentially toxic. We have noted with great interest that in a few patients who have become apparently completely refractory to ganglionic blockade good falls of blood pressure could be obtained still by the sublingual administration of sodium azide. Sodium azide is effective in rare forms of hypertension in man which are thought to be due to a circulating pressor agent and which are refractory to ganglionic blockade. At the present time its use should be confined to clinics undertaking research. It seems most unlikely that the drug will prove satisfactory for the routine treatment of hypertension.

## Organic Di-Azides

Roth and Morphis (1956) studied some organic di-azides of the structure $N_3—(CH_2)_n$ and selected the $n = 7$ compound for special study. Hypotension of several hours duration occurs in dogs after intramuscular administration. The site of action is peripheral. Roth et al. (1956) found that the organic azides were less toxic to rabbits than sodium azide.

## Endocrine Preparations

Borgström (1954) has reported falls of blood pressure in essential hypertension using dimethoxydiethyl-stilboestrol and calcium, sometimes with the addition of testosterone. Dr. Ekehorn kindly wrote to me about this treatment which he found effective. We made a short series of observations but the extent of the blood pressure falls we obtained were not as large as those we have been accustomed to produce with ganglion blocking drugs.

## Pyrogens

It is generally recognized that the administration of bacterial pyrogens may cause large falls of blood pressure (Chasis et al., 1942). Taylor et al. (1949) des[illegible] reactions in the treatment of malignant [illegible] were sometimes severe reactions they o[illegible]papilloedema and apparent reversal of the malignant phase in several patients.

We [225] noted falls of blood pressure using T.A B. injections and, after the pyrogen, noted a considerable increase in hypotensive action of hexamethonium.

### References

1 AAS, K., and THINGSTAD, R. Thiocyanate therapy of hypertension further experiences. Acta med scand., 139. 229, 1951

2 ALLEN, E. V, BANNON, W G., UPSON, M, Jr, HUIZENGA, K. A, BASTRON, J. A, and WAUGH, J M. A new sympatholytic and adrenolytic drug.

42 COLLINS, R. J. The clinical actions of veratrum. *Arch. intern. Med.*, 16: 54, 1915.

42a COMENS, P. Experimental hydralazine disease and its similarity to disseminated lupus erythematosus J. *Lab. clin. Med*, 47: 444, 1956.

43 COMROE, J. H. The location and function of the chemoreceptors of the aorta. Amer. J. Physiol., 127: 176, 1939.

44 CONNELL, W. F, WHARTON, G. K, and ROBINSON, C. E. *Thiocyanate* therapy. Canad. med Ass. J, 62: 20, 1950.

45 CRAMER, W. On the action of veratrum viride with some remarks on the interrelationship of the medullary centres J. Pharmacol, 7: 63, 1915

46 CRAVER, B. N., BARRETT, W, CAMERON, A, and YONKMAN, F. F. The activities of 1-hydrazinophthalazine (Ba-5968), a hypotensive agent. J Amer pharm Ass, 40: 559, 1951.

47 CRAVER, B N., and YONKMAN, F F. Some pharmacological properties of 1-hydrazinophthalazine, a hypotensive agent. Fed. Proc, 9: 265, 1950

48 CROSLEY, A P, CUMMINS, A J, BARKER, H G, and CLARK, J. K. The renal hemodynamic effects of dihydroergocornine (D H O. 180) in man J Pharmacol, 98: 138, 1950

49 CRU[illegible] Jr., [illegible] The [illegible] J. clin Invest., 30, 634, 1951

50 CRUMPTON, C W, KLINGENSMITH, W C, KEFFER, N J, and HAFKENSCHIEL, J H Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects Fed. Proc, 10: 32, 1951

51 DALE, H H On some physiological actions of ergot J. Physiol. (Lond.), 34 163, 1906

52 DAVENPORT, H W. The inhibition of carbonic anhydrase and of gastric acid secretion by thiocyanate Amer J Physiol., 129: 505, 1940.

53 DAVIS, L, TARKINGTON, J, and ANDERSON, R K Physiologic principles underlying the treatment of high diastolic hypertension by thiocyanates and sympathectomy Ann Surg, 133. 867, 1951.

54 DAWES, G S Studies on veratrum alkaloids VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridine. J Pharmacol, 89 325, 1947

55 *DELIUS*, L, HAMMERSCHMIDT, D, and ODENTHAL, F Klinisch-experimentelle Untersuchungen uber die Kreislaufdynamischen Wirkungen der dihydrierten Mutterkornalkaloide Klin Wschr., 27: 33, 1949.

56 DEL SOLAR, A, DUSSAILLANT, G, BRODSKY, M., and LEVY, M Estudio critico del tratamiento medico de la hypertension arterial Rev. méd. Chile, 73 293, 1945

57 DEL SOLAR, A, DUSSAILLANT, G, BRODSKY, M, and LEVY, M. A critical study of the medical treatment of arterial hypertension. Amer. Heart *J, 31 523, 1946*

58 DEUTSCH, E, and MARKOFF, T Mitteilungen zur Nierenclearance. VI. Die Beeinflussung der Nierenleistung durch Hydergin. Klin. Med. (Wien), *3 105, 1953*

59 DE VLEESCHHOUWER, G R. Pharmacology of dibenzyl-$\beta$-chloroethylamine hydrochloride (dibenamine) Proc Soc. exp Biol. (N.Y.), 66: 151, 1947

60 DOMAZLSKI, C A, Jr, KOLB, L C, and HINES, E. A. Jr. Delirious reac-

gine) in the treatment of essential hypertension. Acta med. scand., 145: 189, 1953.

23 BEIN, H. J., GROSS, F., TRIPOD, J., and MEIER, R. Experimentelle Untersuchungen uber die Kreislaufwirkung der blutdrucksenkenden Hydrazinophthalazinderivate Apresoline und Nepresol. Schweiz. med. Wschr., 83: 336, 1953.

24 BEIN, H. J., TRIPOD, J., and MEIER, R. Zur Kreislaufwirkung des 1-Hydrazinophthalazine. Experientia (Basel), 8: 74, 1952.

25 BELLO, C. T., MOSS, W. G., and WEISS, E. Effect of orally administered dihydroergocornine (D.H.O. 180) on hypertension. Amer. J. Med., 8: 634, 1950.

26 BERNARD, C. Leçons sur les effets des substances toxiques et médicamenteuses. Paris, p. 354, 1857.

27 BIRCHER, R., and CERLETTI, A. Pharmakodynamische Grundlagen der Therapie von Kreislaufstörungen mit den Dihydroalkaloiden des Mutterkorns. Helv. med. Acta., suppl 22: 13, 1949.

28 BLACK, M. M., ZWEIFACH, B. W., and SPEER, F. D. Comparison of hypotensive action of sodium azide in normotensive and hypertensive patients Proc. Soc. exp Biol (N Y), 85: 11, 1954.

29 BLUMBERGER, K., Medikamentose Therapie der Hypertonie. Schweiz med. Wschr, 80 : 676, 1950

30 BLUNTSCHLI, H J, and GOETZ, R H The effect of a new sympathicolytic drug (dihydroergocornine) on the blood-pressure with special reference to hypertension. S Afr med J, 21: 382, 1947.

31 BLUNTSCHLI, H J, and GOETZ, R. H The effect of ergot derivatives on the circulation in man with special reference to two new hydrogenated compounds (dihydroergotamine and dihydroergocornine) Amer. Heart J, 35 873, 1948.

32 BLUNTSCHLI, [illegible] fur die [illegible] droergoc[illegible]

33 BORGSTRÖM, S A Endocrine treatment of essential hypertension Acta med scand, suppl, 290: 1954

34 BORISON, H L, and FAIRBANKS, V F Mechanism of veratrum-induced emesis in the cat J Pharmacol, 105 317, 1952

35 BRADLEY, S E, INGELFINGER, F. J, BRADLEY, G P, and CURRY, J. J. The estimation of hepatic blood flow in man J clin Invest, 24: 890, 1945

36 BRIDGES, W C, and WHITE, P D The treatment of diastolic hypertension. Med Clin N Amer, 31 1106, 1947

37 CAPLOVITZ, C D, and MOYER, J H Imadazoline as a hypotensive agent. Amer J Med, 11: 617, 1951

38 CHASIS, H, GOLDRING, W, and SMITH, H W Reduction of blood pressure associated with the pyrogenic reaction in hypertensive subjects J. clin. Invest, 21: 369, 1942

39 CHRISTENSEN, B V, and MCLEAN, A P The bioassay of veratrum viride J. Amer pharm Ass, 25: 414, 1936

40 CLARKE, C. W, Jr, HAYS, D R, Jr., and VAN ITALLIE, T B Clinical appraisal of a new adrenergic blocking agent effect of regitine on digital blood flow in normal subjects and patients with peripheral arterial diseases Circulation (N Y.), 8 715, 1953

41 COE, W. S, BEST, M M, and KINSMAN, J M. Veratrum viride in the treatment of hypertensive vascular disease. J Amer med Ass., 143: 5, 1950.

42 COLLINS, R. J. The clinical actions of veratrum. Arch. intern. Med., 16: 54, 1915
42a COMENS, P. Experimental hydralazine disease and its similarity to disseminated lupus erythematosus. J. Lab. clin. Med., 47: 444, 1956.
43 COMROE, J. H. The location and function of the chemoreceptors of the aorta. Amer. J. Physiol., 127: 176, 1939.
44 CONNELL, W. F., WHARTON, G. K., and ROBINSON, C. E. Thiocyanate therapy. Canad. med. Ass. J., 62: 20, 1950.
45 CRAMER, W. On the action of veratrum viride with some remarks on the interrelationship of the medullary centres. J. Pharmacol., 7: 63, 1915
46 CRAVER, B. N., BARRETT, W., CAMERON, A., and YONKMAN, F. F. The activities of 1-hydrazinophthalazine (Ba-5968), a hypotensive agent. J. Amer. pharm. Ass., 40: 559, 1951.
47 CRAVER, B. N., and YONKMAN, F. F. Some pharmacological properties of 1-hydrazinophthalazine, a hypotensive agent. Fed. Proc., 9: 265, 1950
48 CROSLEY, A. P., CUMMINS, A. J., BARKER, H. G., and CLARK, J. K. The renal hemodynamic effects of dihydroergocornine (D.H.O. 180) in man. J. Pharmacol., 98: 138, 1950
49 CRUMPTON, C. W., FREIDLAND, C. K., KUO, P. T., SCHNABEL, T. G., Jr., FOLTZ, E. L., PAGE, R. G., ALANIS, J., and HAFKENSCHIEL, J. H. The hemodynamic actions of protoveratrine in essential hypertension. J. clin. Invest., 30: 634, 1951
50 CRUMPTON, C. W., KLINGENSMITH, W. C., KEFFER, N. J., and HAFKENSCHIEL, J. H. Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. Fed. Proc., 10: 32, 1951
51 DALE, H. H. On some physiological actions of ergot. J. Physiol. (Lond.), 34: 163, 1906
52 DAVENPORT, H. W. The inhibition of carbonic anhydrase and of gastric acid secretion by thiocyanate. Amer. J. Physiol., 129: 505, 1940.
53 DAVIS, L., TARKINGTON, J., and ANDERSON, R. K. Physiologic principles underlying the treatment of high diastolic hypertension by thiocyanates and sympathectomy. Ann. Surg., 133: 867, 1951.
54 DAWES, G. S. Studies on veratrum alkaloids VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridine. J. Pharmacol., 89: 325, 1947
55 DELIUS, L., HAMMERSCHMIDT, D., and ODENTHAL, F. Klinisch-experimentelle Untersuchungen über die Kreislaufdynamischen Wirkungen der dihydrierten Mutterkornalkaloide. Klin. Wschr., 27: 33, 1949.
56 DEL SOLAR, A., DUSSAILLANT, G., BRODSKY, M., and LEVY, M. Estudio critico del tratamiento medico de la hypertension arterial. Rev. méd. Chile, 73: 293, 1945
57 DEL SOLAR, A., DUSSAILLANT, G., BRODSKY, M., and LEVY, M. A critical study of the medical treatment of arterial hypertension. Amer. Heart J., 31: 523, 1946
58 DEUTSCH, E., and MARKOFF, T. Mitteilungen zur Nierenclearance VI. Die Beeinflussung der Nierenleistung durch Hydergin. Klin. Med. (Wien), 3: 105, 1953
59 DE VLEESCHHOUWER, G. R. Pharmacology of dibenzyl-β-chloroethylamine hydrochloride (dibenamine). Proc. Soc. exp. Biol. (N.Y.), 66: 151, 1947
60 DOMAZLSKI, C. A., Jr., KOLB, L. C., and HINES, E. A. Jr. Delirious reac-

tions secondary to thiocyanate therapy of hypertension. Proc. Mayo Clin., **28**: 272, 1953.

61 DOYLE, A. E., and SMIRK, F. H. The use of the pure veratrum alkaloids neogermitrine and protoveratrine in hypertension. Brit. Heart J., **15**: 439, 1953.

62 DUPUY, H. J., SIGNORELLI, J., and ATTYAH, A. M. Dihydrogenated ergot alkaloids in the treatment of essential hypertension. Circulation (N.Y.), **5**: 285, 1952.

63 ECHAVE, R. K. L'angine de poitrine: Conceptions pathogéniques et traitement sympathicolytique. Cardiologia (Basel), **20**: 129, 1952.

64 ELEK, S. R., MCNAIR, J. D., and GRIFFITH, G. C. The electrocardiographic effects of intravenous veratrum viride. Circulation (N.Y.), **7**: 903, 1953.

65 ESSELLIER, A. F., LUSCHER, W., and MORANDI, L. Hydrazinophthalazine bei Hypertension. Schweiz. med. Wschr., **83**: 340, 1953.

66 EURMAN, G. H. and MENDLOWITZ, M. The effect of prolonged sodium depletion and of hydralazine hydrochloride and hexamethonium bromide on the digital vascular resistance in primary hypertension. Circulation (N.Y.), **9**: 586, 1954.

67 FAIRBANKS, V. F., and BORISON, H. L. Studies on emetic action of veratrum alkaloids in cats. J. Pharmacol., **103**: 343, 1951.

68 FIELD, L. W., and LAVERTY, R., unpublished 1956.

69 FISCHMANN, E. J., and FISCHMAN, A. Thiocyanate in hypertension. Amer. Heart J., **39**: 477, 1950.

70 FRANKE, R., and THIELE, F. Über die perorale medikamentose Dauerbehandlung des chronischen Hochdruckleidens. Medizinische, **50**: 1626, 1953.

71 FREIS, E. D. Veratrum viride and hexamethonium in the treatment of severe diastolic hypertension. Med. Ann. Distr. Columbia, **20**: 297, 1951.

72 FREIS, E. D., and FINNERTY, F. A., Jr. Suppression of vasomotor reflexes in man following 1-hydrazinophthalazine (C-5968). Proc. Soc. exp. Biol. (N.Y.), **75**: 23, 1950.

73 FREIS, E. D., ROSE, J. C., HIGGINS, T. F., FINNERTY, F. A., Jr., KELLEY, R. T., and PARTENOPE, E. A. The hemodynamic effects of hypotensive drugs in man. IV. 1-hydrazinophthalazine. Circulation (N.Y.), **8**: 199, 1953.

74 FREIS, E. D., and STANTON, J. R. A clinical evaluation of veratrum viride in the treatment of essential hypertension. Amer. Heart J., **36**: 723, 1948.

75 FREIS, E. D., STANTON, J. R., FINNERTY, F. A., Jr., SCHNAPER, H. W., JOHNSON, R. L., RATH, C. E., and WILKINS, R. W. The collapse produced by venous congestion of the extremities or by venesection following certain hypotensive agents. J. clin. Invest., **30**: 435, 1951.

76 FREIS, E. D., STANTON, J. R., CULBERTSON, J. W., LITTER, J., and HALPERIN, M. H. The hemodynamic effects of veratrum viride in hypertensive man: studies of arterial pressure, cardiac output, renal and hepatic clearances, peripheral blood flow, "venous tone" and vasomotor reflexes. J. clin. Invest., **27**: 535, 1948.

77 FREIS, E. D., STANTON, J. R., CULBERTSON, J. W., LITTER, J., HALPERIN, M. H., BURNETT, C. H., and WILKINS, R. W. The hemodynamic effects of hypotensive drugs in man. I. Veratrum viride. J. clin. Invest., **28**: 353, 1949a.

78 FREIS, E. D., STANTON, J. R., LITTER, J., CULBERTSON, J. W., HALPERIN, M. H., MOISTER, F. C., and WILKINS, R. W. The hemodynamic effects

of hypotensive drugs in man. II. Dihydroergocornine. J. clin. Invest., 28: 1387, 1949b.

79 Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C., and Wilkins, R. W. Hemodynamic effects of hypotensive agents in man. Amer. J. Med., 7: 414, 1949c.

80 Freis, E. D., Stanton, J. R., and Moister, F. C. Assay in man of the chemical fractions of veratrum viride, and identification of the pure alkaloids germitrine and germidine as potent hypotensive principles derived from the drug. J. Pharmacol., 98: 166, 1950.

81 Freis, E. D., Stanton, J. R., and Wilkins, R. W. The effects of certain dihydrogenated alkaloids of ergot in hypertensive patients. Amer. J. med. Sci., 216: 163, 1948.

82 Gager, L. T. The incidence and management of hypertension, with a note on sulphocyanate therapy. J. Amer. med. Ass., 90: 82, 1928.

82a Galen, W. P. Drug treatment of hypertension. Northw. Med. (Seattle), *54: 1246, 1955*

83 Garvin, C. F. The fatal toxic manifestations of the thiocyanates. J. Amer. med. Ass., 112: 1125, 1939

84 Gast, W., and Huber, E. F. *Ueber die Behandlung der Hypertension mit* Hydergin. Wien. klin. Wschr., 62. *900, 1950*

85 Gibbs, D. F. Dihydrogenated alkaloids of ergot in the investigation and

86 Gill

87 Goetz, R. H. The action of dihydroergocornine on the circulation with special reference to hypertension. Lancet, 1. 510, 1949

88 Goetz, R. H. The effect of sympathicolytic drugs on the cardiovascular system in man with special reference to hypertension. Angiology, 2: 1, 1951

89 Goldman, R., and Frierson, H. R. Effect of veriloid upon renal function when administered in hypotensive doses to patients with arterial hypertension. Amer. J. Med., 14: 168, 1953

90 Goldring, W., and Chasis, H. Thiocyanate therapy in hypertension. I. Observations on its toxic effects. Arch. intern. Med., 49: 321, 1932a.

91 Goldring, W., and Chasis, H. Thiocyanate therapy in hypertension. II. Its effect on blood pressure. Arch. intern. Med., 49: 934, 1932b.

92 Goldstein, F., and Rieders, F. Formation of cyanide in dog and man following administration of thiocyanate. Amer. J. Physiol., 167: 47, 1951

93 Goldstein, M. R., Schloss, W. P., and Cohn, S. H. Bladder disturbance due to apresoline. New Engl. J. Med., 247: 525, 1952.

94 Goodman, L. S., and Gilman, A. The pharmacological basis of therapeutics. The Macmillan Company, New York, 1955.

95 Gourzis, J. T., and Bauer, R. O. The effect of veratrum derivatives on the isolated intestine of the rabbit and on the intact intestine of the trained unanesthetized dog. J. Pharmacol., 103: 471, 1951.

96 Goutier, R. Sensitization to potassium ions and decurarization by some veratrum alkaloids. Brit. J. Pharmacol., 5: 33, 1950.

97 Grayson, J., and Swan, H. J. C. Action of adrenaline, noradrenaline and dihydroergocornine on the colonic circulation. Lancet, 1: 488, 1950.

98 Grimson, K. S., Chittum, J. R., and Metcalf, B. H. Actions of 1-hydrazinophthalazine (C-5968) on vasomotor reflexes and hypertension in dogs and man. Fed. Proc., 9: 279, 1950.

99 Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr., and Sieber, H. A.

Caution with regard to use of hexamethonium and "apresoline". J. Amer. med. Ass., 149: 215, 1952.

100 GROPPER, A. L., SURTSHIN, A., and HEDRICK, J. T. Effects of veriloid on essential hypertension — A new derivative of veratrum viride. Arch. intern. Med., 87: 789, 1951.

101 GROSS, F., DRUEY, J., and MEIER, R. Eine neue Gruppe blutdrucksenkender Substanzen von besonderem Wirkungscharakter. Experientia (Basel), 6: 19, 1950.

102 HAAS, H. T. A. Zur Pharmakologie des Germerins und seiner Spaltprodukte. Arch. exp. Path. Pharmak., 189, 397, 1938.

103 HADORN, W. Über Bluthochdruck. Schweiz med. Wschr., 82: 585, 1952.

104 HAFKENSCHIEL, J. H., CRUMPTON, C. W., MOYER, J. H., and JEFFERS, W. A. The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J clin. Invest., 29: 408, 1950.

105 HAFKENSCHIEL, J H., and FRIEDLAND, C K. The effect of 1-hydrazinophthalazine on cerebral blood flow, vascular resistance, oxygen uptake and jugular oxygen tension in hypertensive subjects. J. clin. Invest, 32: 655, 1953

106 HAFKENSCHIEL, J. H, and LINDAUER, M A. 1-hydrazinophthalazine (apresoline) in the treatment of hypertension· A two-year study. Circulation (N.Y), 7: 52, 1953

107 HAGER, H. Augenhintergrundbefunde bei medikamentoser Behandlung der Hypertonie Zusammenkunft Deut. Ophthal Ges Heidelberg, 57: 302, 1951

108 HAIMOVICI, H, and MEDINETS, H E Effect of dibenamine on blood pressure in normotensive and hypertensive subjects Proc Soc exp. Biol. (N.Y.), 67: 163, 1948

109 HAI

exp. Biol (N Y), 77 477, 1951.

110 HAMMERSCHMIDT, D, and ODENTHAL, F Über die Wirkung der hydrierten Mutterkornalkaloide auf den arteriellen und venösen Blutdruck Z KreislForsch, 39: 150, 1950

111 HAUSS, W. H, KREUZIGER, H, and ASTEROTH, H. Über die Wirkung von Dibenaminhydrochlorid bei Hypertonikern. Dtsch med. Wschr, 74· 1470, 1949a

112 HAUSS, W H, KREUZIGER, H, and ASTEROTH, H Über die Wirkung neuerer sympathicolytischer Substanzen Klin. Wschr, 27 690, 1949b.

113 HEALY, J C Therapeutics and toxicology of the sulphocyanates New Engl J Med, 205· 581, 1931

114 HECHT, H. H., and ANDERSON, R B The influence of dibenamine (N, N-dibenzyl-β-chloroethylamine) on certain functions of the sympathetic nervous system in man Amer J Med, 3· 3, 1947

115 HEDBOM, K Ueber die Einwirkung verschiedener Stoffe auf das isolierte Saugetierherz Skand Arch Physiol, 8 169, 1898

116 HEWLETT, A W The pulse flow in the brachial artery. V The influence of certain drugs. Arch intern. Med., 20· 1, 1917

117 HEYMANS, C., and REGNIERS, P. Influence de l'ergotamine sur les réflexes cardio-vasculaires du sinus carotidien Arch int Pharmacodyn, 36: 116, 1929.

118 HINES, E. A Jr Potassium thiocyanate and sodium nitroprusside Proc. Mayo Clin., 27: 485, 1952

119 HINES, E. A., Jr., and BROWN, G. E. A standard stimulus for measuring

vasomotor reactions: Its application in the study of hypertension. Proc. Mayo Clin., 7: 332, 1932.

120 HOFFMEISTER, W., and KRÜCK, F. Über den Wirkungsmechanismus des Kaliumthiocyanat (Rhodankalium) als Erklärung des depressorischen Effektes beim Hochdruck. Klin. Wschr., 32: 106, 1954.

121 HOLLEY, H. L., and KOFFLER, I. A. Veratrum viride in treatment of hypertension. Amer. Practit. (Philad.), 1: 840, 1950.

122 HOOBLER, S W. Treatment of hypertension. Amer. J. Med., 17: 259, 1954.

123 HOOBLER, S. W., and CORLEY, R. W. The hypotensive action of protoveratrine. Univ. Mich. med. Bull, 16: 362, 1950.

124 HOOBLER, S W, CORLEY, R. W., KABZA, T. G., and LOYKE, H. F. Treatment of hypertension with oral protoveratrine. Ann. intern. Med, 37: 465, 1952.

125 JARISCH, A, and RICHTER, H. Die afferenten Bahnen des Veratrineffektes in den Herznerven. Arch. exp. Path Pharmak., 193: 355, 1939.

126 JOHNSON, C. C. The actions and toxicity of sodium nitroprusside. Arch. int. Pharmacodyn, 35. 480, 1929.

127 JOHNSON, R. P The treatment of hypertension with 1-hydrazinophthalazine (apresoline). Amer. Heart J., 46. 593, 1953

128 JOHNSON, R L, FREIS, E D, and SCHNAPER, H W Clinical evaluation of 1-hydrazinophthalazine (C-5968) in hypertension — With special reference to alternating treatment with hexamethonium. Circulation (N Y), 5: 833, 1952

128a JUDSON, W. E, HOLLANDER, W, and WILKINS, R. W. Observations on angina pectoris during drug treatment of hypertension. Circulation (N Y), 13. 553, 1956

129 KAHN, M A Effect of hydralazine in hypertension. Brit. med. J., 1: 27, 1953

130 KAISER, K, and [illegible] P Über die Wirkung der Dihydroalkaloide des Muterkorns [illegible]

131 KAPPERT, A. U. [illegible] Mutterkornalkaloide bei [illegible] Hypertonie Helv med Acta, suppl 22: 16, 1949.

132 KAPPERT, A, BAUMGARTNER, P, and RUPP, F. Ueber die blutdrucksenkende Wirkung neuer dihydrierter Mutterkornalkaloide. Schweiz med Wschr, 78 1265, 1948

133 KAPPERT, A, SKOGLUND, C H, BERGHOLTZ, A, and NYLIN, G. The effect of hydergin (CCK) on reflex vasoconstriction and reflex blood pressure stimulation Acta med scand, 141: 440, 1952

134 KAUFMAN, M Pancytopenia following use of hydrallazine ("apresoline") — Report of a case J Amer med. Ass, 151: 1488, 1953

135 KAUNTZE, R, and TROUNCE, J. The hypotensive action of veriloid (veratrum viride) — A clinical investigation Lancet, 1: 549, 1951.

136 KIRKENDALL, W M, and CULBERTSON, J. W. Some effects of hexamethonium ($C_6$) and 1-hydrazinopthalazine (HP) on kidney circulation. J Lab clin. Med, 40. 818, 1952.

137 KLEH, J, and FAZEKAS, J. F The use of apresoline in the hypertensive arteriosclerotic syndrome. Amer J. med Sci., 227: 57, 1954.

138 KONZETT, H, and ROTHLIN, E Investigations on the hypotensive effect of the hydrogenated ergot alkaloids. Brit. J Pharmacol, 8: 201, 1953.

139 KRAYER, O, and ACHESON, G A. The pharmacology of the veratrum alkaloids Physiol. Rev., 26. 383, 1946.

140 KRAYER, O, and MENDEZ, R. Studies on veratrum alkaloids. I. The action of veratrine upon the isolated mammalian heart. J. Pharmacol., 74: 350, 1942.

141 KRAYER, O., MOE, G. K., and MENDEZ, R. Studies on veratrum alkaloids. VI. Protoveratrine: Its comparative toxicity and its circulatory action. J. Pharmacol., 82: 167, 1944.

142 KÜHNS, K., and VOGEL, H. Das Elektrokardiogramm im Stehen. Arch.

143 sschwankungen am isolierten . Pflügers Arch. ges. Physiol., 107: 238, 1905.

144 KUMMER, P., and LA ROSÉE, R. Über die Hochdrucktherapie mit Hydrazinophthalazinen. Munch. med. Wschr., 95: 729, 1953.

144a KVALE, W. F. Hypotensive drugs. Minn. Med., 39: 173, 1956.

145 LASCH, F. Zur Frage der Blutdruckwirkung des Hydergins Munch. med. Wschr., 94: 1325, 1952.

146 LAURENCE, D. R., and MILES, N. A. Apresoline intolerance with bladder paralysis. New Engl. J. Med., 248: 464, 1953.

147 LAVIETES, P. H., BOURDILLON, J., and KLINGHOFFER, K. A. The volume of the extracellular fluids of the body. J. clin. Invest., 15: 261, 1936.

148 LE ROY, B. R. The thiocyanates in solution, the natural physiological solvents of the body — A clinical study N. Y. med. J., 90: 802, 1909.

149 LOVEJOY, F. W., YU, P. N. G., BRUSE, R. A., NYE, R. E., WELCH, G., BRODY, B. B., and MUXWORTHY, J. The effects of intravenous protoveratrine on hemodynamics and exercise tolerance in patients with hypertension. Amer. J. med. Sci., 222: 129, 1951.

150 LUETH, H. C., and HANKS, T. G. Unusual reactions of patients with hypertension to glyceryl trinitrate. Arch. intern. Med., 62: 97, 1938.

151 MCCRORY, W. W., and RAPOPORT, M. Effects of a new vasodepressor (apresoline) on blood pressure and renal function in children with acute nephritis. Amer. J. Dis. Child., 84: 642, 1952.

152 MCGREGOR, M., ZION, M., and BOTHWELL, T. H. Oral hydergine in the treatment of hypertension. S. Afr. med. J., 28: 292, 1954.

153 MACKINNON, J. Effect of hypotension-producing drugs on the renal circulation. Lancet, 2: 12, 1952.

154 MAISON, G. L., GOTZ, E., and STUTZMAN, J. W. Relative hypotensive activity of certain veratrum alkaloids. J. Pharmacol., 103: 74, 1951.

155 MAISON, G. L., and STUTZMAN, J. W. A bioassay for veratrum derivatives based on hypotension in dogs. Arch. int. Pharmacodyn., 85: 357, 1951.

156 MARSH, D. F., HERRING, D. A., and HOWARD, A. Veratramine. J. Pharmacol., 103: 172, 1951.

157 MARZONI, F. A., REARDON, M. J., HENDRIX, J. P., and GRIMSON, K. S. A comparison of sympatholytic effects of priscol, etamon, and dibenamine in dogs with results of actual sympathectomy. Surgery, 26: 117, 1949.

158 MEILMAN, E. Clinical studies on veratrum alkaloids. III. The effect of protoveratrine on renal function in man. J. clin. Invest., 32: 80, 1953.

159 MEILMAN, E., and KRAYER, O. Clinical studies on veratrum alkaloids. I. The action of protoveratrine and veratridine in hypertension. Circulation (N.Y.), 1: 204, 1950.

160 MEILMAN, E., and KRAYER, O. Clinical studies on veratrum alkaloids. II. The dose-response relations of protoveratrine in hypertension. Circulation (N.Y.), 6: 212, 1952.

161 MELCHINGER, G., SARRE, H., WALZ, L., and ZIMMERMANN, G. Über die Behandlung der Hypertonie mit Rhodan. Dtsch. med. Wschr., 77: 990, 1952.

162 MILLS, L. C., and MOYER, J. H. Treatment of hypertension with orally and

parenterally administered purified extracts of veratrum viride. Arch. intern. Med., 90: 587, 1952.

163 Moe, G. K., Bassett, D. L., and Krayer, O. Studies on veratrum alkaloids. V. The effect of veratridine and cevine upon the circulation in anesthetized dogs, with particular reference to femoral arterial flow. J. Pharmacol., 80: 272, 1944.

164 Moister, F. C., Stanton, J. R., and Freis, E. D. Observations on the development of tolerance during prolonged oral administration of dihydroergocornine. J. Pharmacol., 96: 21, 1949.

165 Moran, N. C., Dresel, P. E., Perkins, M. E., and Richardson, A. P. The pharmacological actions of andromedotoxin, an active principle from rhododendron maximum. J. Pharmacol., 110: 415, 1954a.

166 Moran, N. C., Perkins, M. E., and Richardson, A. P. The action of andromedotoxin on the carotid sinus in dogs. J. Pharmacol., 111: 454, 1954b.

167 Morrow, J. D., Schroeder, H. A., and Perry, H. M. Studies on the control of hypertension by hyphex. II. Toxic reactions and side effects. Circulation (N.Y.), 8: 829, 1953.

168 Moser, M., Syner, J., Malitz, S., and Mattingly, T. Acute psychosis as a complication of hydrallazine therapy in essential hypertension. J. Amer. med. Ass., 152: 1329, 1953.

169 Moser, M., Walters, M., Master, A., Taymor, R. C., and Metraux, J. Chemical blockade of the sympathetic nervous system in essential hypertension. Arch. intern. Med., 89: 708, 1952.

170 Mosey, L., and Kaplan, A. Respiratory effects of potent hypotensive derivatives of veratrum. J. Pharmacol., 104: 67, 1952.

171 Mosey, L., Maison, G. L., and Stutzman, J. W. Cardiac effects of a hypotensive veratrum derivative in dogs premedicated with digitalis or quinidine. Proc. Soc. exp. Biol. (N.Y.), 76: 486, 1951.

172 Moyer, J. H. Hydrallazine (apresoline) hydrochloride: Pharmacological observations and clinical results in the therapy of hypertension. Arch. intern. Med., 91: 419, 1953.

173 Moyer, J. H., and Caplovitz, C. The clinical results of oral and parenteral administration of 2-(N'p-tolyl-N'-m-hydroxyphenylaminoethyl) imidazoline hydrochloride (regitine) in the treatment of hypertension and an evaluation of the cerebral hemodynamic effects. Amer. Heart J., 45: 602, 1953.

174 Moyer, J. H., and Handley, C. A. Renal function and systemic blood pressure changes following the administration of hydrazinophthalazine. J. Lab. clin. Med., 36: 969, 1950.

175 Moyer, J. H., and Handley, C. A. Renal hemodynamic and blood pressure response to n-phenoxyisopropyl-n-benzyl-β-chlorethylamine (SKF 688A). J. Pharmacol., 104: 329, 1952.

176 Moyer, J. H., Handley, C. A., and Huggins, R. A. Some pharmacodynamic effects of 1-hydrazinophthalazine (C-5068) with particular reference to renal function and cardiovascular response. J. Pharmacol., 103: 368, 1951.

177 Nichols, J. B. The pharmacologic and therapeutic properties of the sulphocyanates. Amer. J. med. Sci., 170: 735, 1925.

178 Nickerson, M., and Goodman, L. S. Pharmacological properties of a new adrenergic blocking agent: N,N-dibenzyl-β-chloro-ethylamine (dibenamine). J. Pharmacol., 89: 167, 1947.

179 Nickerson, M., and Nomaguchi, G. M. Responses to sympathomimetic amines after dibenamine blockade. J. Pharmacol., 107: 284, 1953.

180 NUZUM, F. R. The dihydrogenated ergot alkaloids in the treatment of essential hypertension. Ann. west. Med. Surg., 4: 781, 1950.
181 NYMAN, E. Experiences with perorally induced "adrenergic block" — Clinical studies on the effect of a highly active β-halo-alkylamine Acta med. scand., 147: 417, 1954.
182 OSGOOD, C. Observations on the medicinal properties of the veratrum viride. Amer. J. med. Sci., 16: 296, 1835.
183 PAGE, I. H. Treatment of essential and malignant hypertension. J. Amer. med. Ass., 147: 1311, 1951.
184 PAGE, I. H. Neural and humoral control of blood vessels A Ciba Foundation Symposium on Hypertension. J. & A. Churchill Ltd., London, 1954.
185 PAGE, I. H., CORCORAN, A. C., DUSTAN, H. P., and KOPPANYI, T. Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. Circulation (N.Y.), 11: 188, 1955.
186 PAPACOSTAS, C. A., MOUNTAIN, C. F., MAISON, G. L., and BAUER, R. O. Influence of anesthesia on the hypotensive and bradycardic action of veratrum. Fed. Proc., 11: 381, 1952.
187 PAULI, W. Ueber Ionenwirkungen und ihre therapeutische Verwendung. Münch. med. Wschr., 50: 153, 1903.
188 PERRY, H. M. Chemical observations on 1-hydrazinophthalazine. J clin. Invest , 32: 595, 1953.
189 PERRY, H M., and SCHROEDER, H. A. Studies on the control of hypertension by hyphex. III. Pharmacological and chemical observations on 1-hydrazinophthalazine. Amer. J. med. Sci., 228· 396, 1954
190 PINES, K. L , and PERERA, G. A. Thiocyanate effect on sodium excretion in normotensive and hypertensive subjects Proc Soc. exp. Biol. (N.Y.), 81: 149, 1952.
191 PROCHNIK, G., MAISON, G L , and STUTZMAN, J. W. Carotid-occlusion-pressor reflex: Influence of existing mean arterial pressure, of anesthetics and of ganglionic- and adrenergic-blocking drugs Amer. J. Physiol., 162. 553, 1950.
192 PRUSIK, B Les sympathicolytiques en pratique clinique. Rev. méd Liège, 3: 677, 1948
193 RENZI, A A., GILMAN, M , and GAUNT, R Diuretic action of pyribenzamine. Fed Proc., 13: 117, 1954
194 REUBI, F L'action de quelques dérivés de l'ergot de seigle sur la circulation rénale Experientia (Basel), 5. 296, 1949
195 REUBI, F C Renal hyperemia induced in man by a new phthalazine derivative. Proc Soc. exp Biol (N Y ), 73. 102, 1950
196 RICHARDS, C E., BROCKHURST, R J., and COLEMAN, T. H. Thiocyanate goiter with myxedema — Report of two cases J clin Endocr , 9: 446, 1949
197 RICHARDSON, A. P , FARRAR, C , and WALKER, H. A Effect of veratrine alkaloids on the carotid sinus pressor reflex. Fed Proc , 10· 331, 1951.
198 RIVEN, S. S , POCOCK, D. G., KORY, R C , ROEHM, D C , ANDERSON, R S , and MENEELY, G R The control of hypertension with 1-hydrazionphthalazine (apresoline) Amer. J Med , 14· 160, 1953
198a ROTH, L. W , and MORPHIS, B B Activity relationships in animals of a series of organic di-azides. Fed Proc , 15: 477, 1956.
198b ROTH, F. E., SCHURR, J., MOUTIS, E , and GOVIER, W M Comparative hypotensive effects and toxicity of sodium azide and selected organic azides. J. Pharmacol , 116. 50, 1956
199 ROTHLIN, E. Recherches expérimentales sur l'ergotamine, alcaloïde spécifique de l'ergot de seigle Arch. int. Pharmacodyn , 27: 459, 1923.

200 ROTHLIN, E. Ueber die adrenergischen Funktionen am Herz und an Gefässen Bull. schweiz. Akad. med Wiss., 1: 194, 1945

201 ROTHLIN, E Pharmacology of natural and dihydrogenated alkaloids of ergot. Bull. schweiz Akad med. Wiss., 2: 249, 1946a.

202 ROTHLIN, E. Zur Pharmakologie des sympathicolyticums Dihydroergotamin dhe 45 Schweiz. med. Wschr., 76: 1254, 1946b.

203 ROTHLIN, E. Zur Analyse der Blutdruckwirkung der natürlichen und dihydrierten Mutterkornalkaloide Experientia (Basel), 5: 79, 1949.

204 ROTHLIN, E., and CERLETTI, A. Beitrag zum Problem sog. kompetitiver pharmakodynamischer Effekte. Arch. int. Pharmacodyn., 82: 118, 19[illegible]

205 ROTHLI[illegible] ko[illegible]

206 ROTHLIN, E., and CERLETTI, A. Über einige [illegible] suchungen an Mäusen mit congenitaler Drehsucht. Helv. physiol. pharmacol Acta, 10 319, 1952

207 RUBIN, B, and BURKE, J C Bioassay of veratrum viride. I. Effect of veratryl on carotid sinus pressor reflex J. Pharmacol, 105: 409, 1952

208 RUSKIN, A, and MCKINLEY, W F. Comparative study of potassium thiocyanate and other drugs in the treatment of essential hypertension. Amer Heart J, 34 691, 1947

209 RUSKIN, A., and RIDER, J A Veratrum viride (bioassayed) in the treatment of essential hypertension Tex St J Med., 46: 60, 1950

210 SAINT-PIERRE, H, CORCORAN, A C., TAYLOR, R. D., and DUSTAN, H. P. Relief of hypertensive headache by intravenous injection of thiocyanate J Amer med. Ass, 152· 493, 1953.

211 SAPHIRE, E J A clinical evaluation of oral veriloid in the treatment of hypertensive disease Ann intern Med, 41: 1211, 1954.

212 SARRE, H Klinik und Therapie der Hyper- und Hypotonie. Verh. dtsch. Ges KreislForsch, 15 137, 1949

213 SCHEINBERG, I H, and KOWALSKI, H J The binding of thiocyanate to albumin in normal human serum and defibrinated blood with reference to the determination of "thiocyanate space". J clin. Invest., 29 475, 1950

214 SCHIMERT, G Jr, and ZICKGRAF, H Zur Therapie der angina pectoris mit dihydrierten Mutterkornalkaloiden (CCK 179) Klin. Wschr., 27: 59, 1949

215 SCHNEIDER, M, and WIEMERS, K Über die Wirkung der hydrierten Mutterkornalkaloide auf die Gehirndurchblutung Klin. Wschr., 29. 580, 1951

216 SCHRECK, W Hochdruckbehandlung mit Hydergin. Med Mschr, 6: 455, 1952

217 SCHROEDER, H A The antihypertensive influence of certain sulfhydryl compounds Science, 114 441, 1951

218 SCHROEDER, H A The effect of 1-hydrazinophthalazine in hypertension. Circulation (N.Y), 5 28, 1952a.

219 SCHROEDER, H A Control of hypertension by hexamethonium and 1-hydrazinophthalazine Arch intern Med., 89· 523, 1952b.

220 SCHROEDER, H A Hypertensive diseases Henry Kimpton, London, 1953.

221 SHAPIRO, A P, BRUST, A A, and FERRIS, E B. A comparative study of the effects of veratrum viride and tetraethylammonium chloride in hypertension Ann. intern Med, 36 607, 1952.

222 SHAPIRO, A P, and FERRIS, E. B. The effects of intravenously administer-

ed veratrum viride in hypertensive and normotensive subjects. Ann. intern. Med., 36: 792, 1952.

223 SHAPIRO, A. P., and GROLLMAN, A. A critical evaluation of the hypotensive action of hydrallazine, hexamethonium, tetraethylammonium and dibenzyline salts in human and experimental hypertension. Circulation (N.Y.), 8: 188, 1953.

224 SHAW, W. M, PAPPER, E. M., and ROVENSTINE, E. A. The influence of dibenamine upon circulatory reactions to ephedrine and neosynephrine in normal man. J. Lab. clin. Med., 34: 669, 1949.

225 SMIRK, F. H. Unpublished observations.

226 SMIRK, F. H., and CHAPMAN, O. W. Comparison of the effects of veratrum alkaloids and of hexamethonium bromide upon the blood pressure in arterial hypertension. Amer. Heart J., 43: 586, 1952.

227 SMITH, A. G., and RUDOLF, R. D. The use of sulphocyanate of soda in high blood pressure. Canad. med. Ass. J., 19: 288, 1928

228 SPÜHLER, O. Neue Wege in der medikamentösen Therapie der Sympathicuserkrankungen. Praxis, 37: 557, 1948.

229 STEARNS, N. S., and ELLIS, L. B. Acute effects of intravenous administration of a preparation of veratrum viride in patients with severe forms of hypertensive disease. New Engl. J. Med, 246: 397, 1952.

230 STEARNS, N. S., and MAISON, G. L. The action of veriloid upon the isolated mammalian heart J. Pharmacol., 100: 238, 1950

231 STOLL, A., and HOFFMANN, A. Die dihydroderivate der natürlichen linksdrehenden mutterkornalkaloide. Helv chim. Acta, 26: 2070, 1943.

232 STUNKARD, A. J., EURMAN, G. H., WACHSPRESS, M., and WERTHEIM, A. R. Treatment of hypertensive disease with hydralazine — Comparison of its action with that of low sodium diet in hospitalized patients. Amer J. Med., 17: 712, 1954.

233 STUTZMAN, J. W., and MAISON, G. L. Hypotensive action of veriloid, an extract of veratrum viride. Fed Proc., 9: 318, 1950.

234 STUTZMAN, J W, MAISON, G. L., and KUSSEROW, G. W. Veriloid, a new hypotensive extract of veratrum viride Proc Soc. exp. Biol (N.Y.), 71: 725, 1949.

235 STUTZMAN, J. W., SIMON, H, and MAISON, G. L Role of vagus nerves in depressor action of veratrum derivatives J. Pharmacol, 101: 310, 1951

236 SUTTON, G. C, BUCKINGHAM, W., BROWN, R. D., and SUTTON, D. C. A clinical evaluation of the treatment of hypertension with dihydrogenated ergotoxine alkaloids. Amer. Heart J., 44: 622, 1952

237 SUTTON, G. C., CERLETTI, A., and TAESCHLER, M Comparative analysis of the effect of hydrogenated ergot alkaloids upon presso- and chemoreceptive reflexes in the cat Arch. int Pharmacodyn, 84. 393, 1950.

238 SWISS, E. D. The emetic properties of veratrum derivatives. J. Pharmacol, 104: 76, 1952

239 TANDOWSKY, R M The clinical effect of dihydroergocornine methanesulphonate (DHO-180) in arterial hypertension. A preliminary report. Circulation (N Y.), 1: 686, 1950

240 TANDOWSKY, R M Clinical evaluation of combined hydrogenated ergot alkaloids (hydergine) in arterial hypertension with special reference to their action in central manifestations Circulation (N Y), 9: 48, 1954.

241 TAYLOR, R, CORCORAN, A. C, and PAGE, I H Further experience with bacterial pyrogens in the treatment of malignant hypertension. J Lab. clin. Med, 34: 1756, 1949.

242 TAYLOR, R. D., DUSTAN, H. P, CORCORAN, A C, and PAGE, I H. Evalua-

tion of 1-hydrazinophthalazine (apresoline) in treatment of hypertensive disease. Arch. intern. Med., 90: 734, 1952.

243 TAYLOR, R. D., and PAGE, I. H. Further studies of the cerebral chemoreceptor buffers as influenced by vasoconstrictor and vasodilator drugs and veratrum viride. Circulation (N.Y.), 4. 184, 1951.

244 TAYLOR, R. D., PAGE, I. H., and CORCORAN, A. C. A hormonal neurogenic vasopressor mechanism. Arch. intern. Med., 88: 1, 1951.

245 THOMAS, C. B. What is the mode of action of thiocyanate compounds in essential hypertension? Ann. intern. Med., 37: 106, 1952.

246 TOURNIAIRE, GUYOT and MORETEAU. Le traitement de l'hypertension artérielle par l'hydergine Lyon med., 186: 113, 1952.

247 VAN DER KOLK, K., DONTAS, A. S., and HOOBLER, S. W. Renal and hypotensive effects of acute and chronic oral treatment with 1-hydrazinophthalazine (apresoline) in hypertension. Amer. Heart J., 48: 95, 1954

248 VAN PROOSDIJ-HARTZEMA, E. G., and DE JONGH, D. K. Investigations into experimental hypertension — III. Dosage and effect of drugs in experimental renal hypertension in the rat. Acta physiol. pharmacol. neerl., 4. 160, 1955

249 VOLKER, R., and KACZMAREK, E. Die Kreislaufwirkungen des Hydergins (CCK 179) beim Hochdruck. Z KreislForsch., 39. 85, 1950.

250 VON BEZOLD, A., and HIRT, L. Über die physiologischen Wirkungen des essigsauren Veratrins Untersuch. Physiol Lab., Wurzburg, pt. 1, 73, 1867.

251 VON EULER, U S Reflektorische und zentrale Wirkung von Kaliumionen auf Blutdruck und Atmung Skand. Arch Physiol., 80: 94, 1938.

252 VON EULER, U. S., and HESSER, C M. Beobachtungen uber hemmungen der Sinusdruckreflexe durch Ergotamin dihydroergotamin und Hyperventilation. Schweiz med. Wschr., 77· 20, 1947.

253 VON EULER, U S., and SCHMITERLÖW, C G The action of ergotamine on the chemical and mechanical reflexes from the carotid sinus region. Acta physiol scand., 8 122, 1944

254 WALD, M H., FIERRO, M I., and KEETON, K H. Toxic effects of 1-hydrazinophthalazine in ambulatory hypertensive patients Amer. Heart J., 46 861, 1953

255 WALD, M H., LINDBERG, H A., and BARKER, M. H. The toxic manifestations of the thiocyanates. J Amer med Ass., 112. 1120, 1939.

256 WALKER, H A., WILSON, S., ATKINS, E C., GARRETT, H. E., and RICHARDSON, A P The effect of 1-hydrazinophthalazine (C-5968) and related compounds on the cardiovascular system of dogs. J. Pharmacol., 101 368, 1951.

257 WATKINSON, G., and EVANS, G Potassium thiocyanate in the treatment of hypertension Brit. med J., 1· 595, 1947.

257a WAUD, R A., LANSING, A M., and LEWIS, R. A The effects of veratrum, dibenzyline and hexamethonium on blood pressure as studied with an artificial heart-lung J Pharmacol., 114· 271, 1955.

258 WEDD, A M Veratrum viride in auricular fibrillation. Heart, 12: 307, 1925

259 WEISS, S., WILKINS, R W., and HAYNES, F. W The nature of circulatory collapse induced by sodium nitrite J. clin Invest., 16. 73, 1937.

260 WERKÖ, L., and LAGERLÖF, H The effect of dihydroergotamine and dihydroergocornine on cardiac output and blood pressure in hypertension Cardiologia (Basel), 15· 120, 1949.

261 WILBRANDT, R Kurze Mitteilung uber die Wirkung von Hydergin-sublingualtabletten bei Hypertonie Praxis, 41: 384, 1952.

262 WILBRANDT, R. Treatment of hypertension with hydergine: Review of 200 cases. Angiology, 4: 183, 1953.
263 WILKINS, R. W. Personal communication. Cited by Johnson, R. P, Amer. Heart J., 46: 593, 1953.
264 WILKINS, R. W. Veratrum viride and essential hypertension. New Engl. J. Med., 242: 535, 1950.
265 WILKINS, R. W. Veratrum viride in hypertensive cardiovascular disease Mod. Conc. cardiovas. Dis., 20: 89, 1951.
266 WILKINS, R. W., and CULBERTSON, J. W. Effects of surgical sympathectomy upon certain vasopressor responses in hypertensive patients. Trans. Ass Amer. Phys., 60: 195, 1947.
267 WILKINS, R. W., FREIS, E. D., and STANTON, J. R. Essential hypertension: Laboratory studies in human beings with drugs recently introduced J. Amer. med. Ass., 140: 261, 1949.
268 WILKINS, R. W., HAYNES, F. W, and WEISS, S. The role of the venous system in circulatory collapse induced by sodium nitrite J. clin. Invest, 16. 85, 1937.
269 WILKINSON, E. L., BACKMAN, H., and HECHT, H. H. Cardiovascular and renal adjustments to a hypotensive agent (1-hydrazinophthalazine: Ciba BA-5968: Apresoline) J. clin. Invest, 31: 872, 1952.
270 WILLIAMS, R. H, JAFFE, H, and TAYLOR, J A Effects of halides, thiocyanate and propylthiouracil upon the distribution of radioiodine in the thyroid gland, blood and urine Amer J med. Sci., 219: 7, 1950.
271 WILLSON, J. R, and SMITH, R. G. The peripheral circulatory action of veratrum viride. J. Pharmacol., 79: 208, 1943
272 WOODWARD, D. J., HOOBLER, S W., and NICKERSON, M. Effect of dibenzyline (SKF 688A) on peripheral blood flow in man. Fed Proc, 11: 404, 1952.
273 WRIGHT, S Studies of reflex activity in involuntary nervous system. II Action of ergotamine on vaso-motor reflexes. J. Physiol. (Lond), 69. 331, 1930.
274 WUNSCH, R. E, WARNKE, R D., and MYERS, G. B. The effects of dibenamine on severe hypertension. Ann intern. Med, 33: 613, 1950.
275 YONKMAN, F F Adrenergic blockade. Mod Med. (Minn.), March, 146, 1953.
276 YOUMANS, W B, and RANKIN, V M Effects of dibenamine on cardiovascular actions of epinephrine, acetylcholine, pitressin and angiotonin in unanesthetized dogs. Proc. Soc exp Biol. (N.Y.), 66: 241, 1947.
277 ZICKGRAF, H Die Wirkung der dihydrierten Mutterkornalkaloide auf den Kreislauf Z klin Med, 145 34, 1949

CHAPTER XVII

# THE RAUWOLFIA ALKALOIDS

The genus, *Rauwolfia*, derives its name from Leonard Rauwolf, a German physician and botanist, who journeyed to Asia and Africa in the years 1573—1575 with the object of studying medicinal plants [illegible]. A hundred and seventy-five species of the genus have been described and one of them in particular, *Rauwolfia serpentina*, with a long snake-like root, has long been used as a medicinal agent in India, Malay and Java. Dr. Nathan Hodges is stated to have found snake root the most effective [illegible] in combating the plague in London (1665). In the Eas [illegible] ment of [illegible] India. I [illegible] dative [illegible] in insanity and in hypertension and noted that there was a fall in blood pressure which, however, might not be established until after some weeks of treatment. They also gave an account of the pharmacology. In the same year Siddiqui and Siddiqui described five of the alkaloids of *Rauwolfia serpentina*. In the subsequent years many publications came from Indian chemists and physicians. In 1949 Vakil published his experiences in the British Heart Journal and within the next few years interest in the alkaloids of *Rauwolfia* became widespread.

## Alkaloids of Rauwolfia

At least twenty alkaloids derived from plants of the *Rauwolfia* genus have been described and several of them exhibit pharmacological activity Pharmacological studies on these alkaloids are far from complete, but it is clear that not all the active substances are *hypotensive* agents. Our own observations have convinced us that there are [illegible]

[illegible] or of mixed alkaloids are derived from *Rauwolfia serpentina*. Among commercial lots offered on the American market Youngken (1954) has identified the roots of other varieties of *Rauwolfia*. Several varieties contain active alkaloids and sometimes, as in *Rauwolfia canescens*, an alkaloid which is not present in *Rauwolfia serpentina*. Even plants of

262 WILBRANDT, R. Treatment of hypertension with hydergine: Review of 200 cases. Angiology, 4: 183, 1953.
263 WILKINS, R. W. Personal communication. Cited by Johnson, R. P., Amer. Heart J., 46: 593, 1953.
264 WILKINS, R. W. Veratrum viride and essential hypertension. New Engl. J. Med., 242: 535, 1950.
265 WILKINS, R. W. Veratrum viride in hypertensive cardiovascular disease. Mod. Conc. cardiovas. Dis., 20: 89, 1951.
266 WILKINS, R. W., and CULBERTSON, J. W. Effects of surgical sympathectomy upon certain vasopressor responses in hypertensive patients. Trans. Ass. Amer. Phys, 60: 195, 1947.
267 WILKINS, R W., FREIS, E. D, and STANTON, J R. Essential hypertension: Laboratory studies in human beings with drugs recently introduced J. Amer. med. Ass., 140: 261, 1949.
268 WILKINS, R. W, HAYNES, F. W, and WEISS, S. The role of the venous system in circulatory collapse induced by sodium nitrite. J. clin. Invest, 16: 85, 1937.
269 WILKINSON, E. L., BACKMAN, H, and HECHT, H H Cardiovascular and renal adjustments to a hypotensive agent (1-hydrazinophthalazine: Ciba BA-5968: Apresoline) J clin. Invest, 31: 872, 1952
270 WILLIAMS, R. H., JAFFE, H., and TAYLOR, J. A. Effects of halides, thiocyanate and propylthiouracil upon the distribution of radioiodine in the thyroid gland, blood and urine Amer. J med Sci, 219: 7, 1950.
271 WILLSON, J. R., and SMITH, R. G. The peripheral circulatory action of veratrum viride. J. Pharmacol, 79. 208, 1943
272 WOODWARD, D. J., HOOBLER, S. W., and NICKERSON, M. Effect of dibenzyline (SKF 688A) on peripheral blood flow in man Fed Proc, 11. 404, 1952
273 WRIGHT, S. Studies of reflex activity in involuntary nervous system. II Action of ergotamine on vaso-motor reflexes J. Physiol. (Lond), 69 331, 1930
274 WUNSCH, R E, WARNKE, R D, and MYERS, G. B The effects of dibenamine on severe hypertension Ann intern Med, 33: 613, 1950.
275 YONKMAN, F F. Adrenergic blockade. Mod Med. (Minn.), March, 146, 1953
276 YOUMANS, W B, and RANKIN, V M Effects of dibenamine on cardiovascular actions of epinephrine, acetylcholine, pitressin and angiotonin in unanesthetized dogs Proc Soc exp. Biol (N.Y.), 66. 241, 1947.
277 ZICKGRAF, H Die Wirkung der dihydrierten Mutterkornalkaloide auf den Kreislauf Z klin Med, 145· 34, 1949.

With moderate doses at least, oral absorption is efficient. Very large doses have been tolerated without risk to life.

*Circulatory effects of reserpine.*

Effect on blood pressure. Most laboratory animals show moderate falls of blood pressure following intravenous or oral administration of reserpine. The extent of the fall is variable and depends to some extent on the conditions of the experiment being, for example, greater in anaesthetized than in unanaesthetized rabbits. There is some variability in the rate of onset and subsequent course of the blood pressure fall. With intravenous administration there may be a prompt decrease commonly followed by an additional slow fall afterwards, which may reach a minimum in one to three hours. The relative magnitudes of the immediate and delayed falls vary somewhat according to the animal used. The doses used in such experiments are commonly between 0.25 and 4 mg /kg [60, 103]. The blood pressure falls are not appreciably influenced by posture [61, 75]. Continued administration does not appear to give rise to drug toleration.

Experimental hypertension in the rat has been antagonized to some extent by reserpine. Gaunt et al. (1954) produced hypertension by cortisone and found the blood pressure rise could be prevented to a large extent by reserpine. Some effect was also demonstrated on hypertension induced by the administration of DOCA in combination with unilateral nephrectomy and an increased salt intake. De Jongh and Proosdij-Hartzema (1955) lowered the blood pressure with small quantities but raised it with large doses, in rats with clipped kidney hypertension. Hodge and McQueen (1956) have been able to reduce the blood pressures of renal hypertensive rats to near normal levels by reserpine and by hydrogenated ergot alkaloids.

Effect on pressor reflexes The responses to several pressor reflexes are reduced by the administration of reserpine but to demonstrate this effect it may be necessary to wait one or two hours after intravenous administration until full reserpine action has had time to develop The pressor responses to carotid artery occlusion in the cat [60, 86], to stimulation of the afferent fibres of the vagus nerve in the cat [60] (Fig XVII 1) and to sciatic stimulation in the dog [75] have all been decreased to some extent by the reserpine

The responses are not identical in all animals. We (McQueen, Doyle and Smirk, 1955) found that whereas in the cat afferent vagus stimulation caused a striking pressor response before reserpine and a smaller or reversed response after, the response in the rabbit was different. In the rabbit there was usually a slight pressor response to afferent vagus stimulation which was increased and associated with tachycardia after reserpine administration.

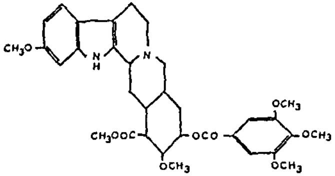
the same variety exhibit differences when grown in different districts.

## EXPERIMENTAL PHARMACOLOGY

Much of the pioneer work on *Rauwolfia* alkaloids was done in India on mixed alkaloidal preparations. Information is becoming available on the activity of the pure alkaloids, to which reference will now be made.

### Reserpine (Serpasil)

Reserpine is responsible for much of the pharmacological activity of preparations from *Rauwolfia serpentina.* The alkaloid was isolated by Müller, Schlittler and Bein (1952) and its formula was suggested by Dorfman et al. (1953). It is a white, sparingly soluble substance but can be dissolved in a 1:1:2 mixture of ethyl alcohol, propylene glycol and water [75], and in various organic acids.




RESERPINE

In most laboratory animals and in man, reserpine affects the central nervous system activity leading to states of drowsiness, tranquillity, calmness and indifference, which are associated with an inhibition of the central connections of the sympathetic nervous system causing falls of blood pressure, bradycardia, miosis and certain other autonomic effects

There is also a peripheral depressing action upon the smooth muscle of blood vessels which may account for a part of the blood pressure fall and the muscle of the intestine and rat diaphragm may be affected by the drug.

Stern et al., (1956) think that the "thyrotoxicosis from fear" in wild rabbits, which is accompanied by exophthalmos, is relieved by 0.05 mg. of reserpine per kg. daily. They think the effect is probably on the hypothalamus. Egdahl et al. (1956) find evidence of a marked increase of adrenocortical secretion in dogs following the intravenous administration of 5 mg. doses. They thought this might be due to increased secretion of ACTH.

With moderate doses at least, oral absorption is efficient. Very large doses have been tolerated without risk to life.

*Circulatory effects of reserpine.*

**Effect on blood pressure.** Most laboratory animals show moderate falls of blood pressure following intravenous or oral administration o[illegible] [illegible] extent of the fall is variable and depends to some extent [illegible] example greater in ana[illegible] variability in the rate of onset and subsequent [illegible] pressure fall. With intravenous administration there may be a prompt decrease commonly followed by an additional slow fall afterwards, which may reach a minimum in one to three hours. The relative [illegible] delayed falls vary somewhat accord- [illegible]

not appreciably [illegible] does not appear to give rise to drug toleration.

Experimental hypertension in the rat has been antagonized to some extent by reserpine. Gaunt et al. (1954) produced hypertension by [illegible] blood pressure rise could be prevented to a [illegible]

and Proosdij-Hartzema [illegible] lowered the blood pressure [illegible] quantities but raised it [illegible] hypertension. Hodge and [illegible] blood pressures of renal hypertensive rats to near normal levels by reserpine and by hydrogenated ergot alkaloids.

**Effect on pressor reflexes.** The responses to several pressor reflexes are reduced by the administration of reserpine but to demonstrate this effect it may be necessary to wait one or two hours after intravenous administration until full reserpine action has had time to develop. The pressor responses to carotid artery occlusion in the cat [60, 66], to stimulation of the afferent fibres of the vagus nerve in the cat [60] (Fig. XVII 1) and to sciatic stimulation in the dog [75] have all been decreased to some extent by the reserpine.

The responses are not identical in all animals. We (McQueen, Doyle and Smirk, 1955) found that whereas in the cat afferent vagus stimulation caused a striking pressor response before reserpine and a smaller or reversed response after, the response in the rabbit was different. In the rabbit there was usually a slight pressor response to afferent vagus stimulation which was increased and associated with tachycardia after reserpine administration.

The response to injections of adrenaline was increased following the administration of reserpine [60].

**Effect on heart rate and rhythm.** It is generally agreed that reserpine slows the heart rate [75]. In dogs this bradycardia appears to be of sinus origin and is unassociated with electrocardiographic change and can be antagonized by atropine [75].

According to Moyer (1954) there is no consistent change in the cardiac output of dogs after reserpine, even when the blood pressure falls.

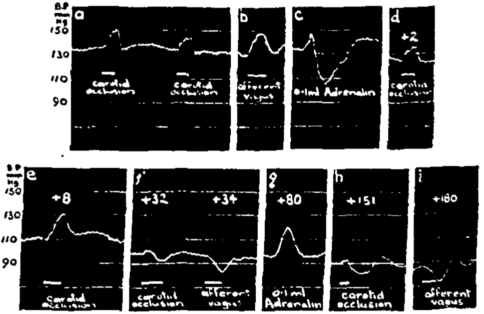



Fig. XVII 1

Cat, 3.5 Kg Chloralose Blood pressure record, left femoral artery. a, b and c show responses to stimuli before administration of reserpine, d to i the responses to the same stimuli after reserpine Between c and d, 2.5 mg. reserpine injected intravenously. [illegible]
F. H., Circulation, 11 · 161-169, 1955, by permission).

**Evidence of a central site of action.** The suggestion has been made that the autonomic actions of reserpine are due to effects on the hypothalamus and that changes in the temperament and activity of animals, with somnolence and lessened aggression, may be due in part or entirely to hypothalamic effects. Schneider (1955) notes the suppression of the manifestations of sham rage in cats. Increase in appetite and gain of weight might also be of hypothalamic origin.

The absence of ganglion blocking action [3, 5], of peripheral sympatholytic action [3, 5], and of peripheral parasympathetic action [3, 5] makes it likely that the sympatholytic inhibition is of central origin. The inhibition of various vasomotor reflexes which has been referred

to already may also be explained
Other autonomic effects which c
higher autonomic centres are miosis, ptosis,
ing membrane, lowering of the body temperature, increase in gastric secretion and increase in intestinal motility.

Additional evidence that some of the autonomic effects of reserpine arise from parts of the nervous systems higher than the medulla is provided by an experiment of Bein (1955). Bein showed that when the brain is severed immediately caudal to the quadrigeminal bodies, much

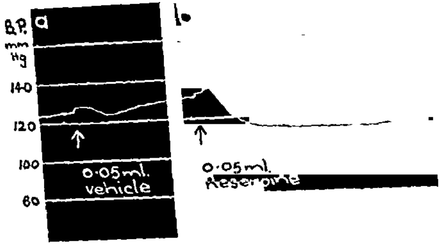



FIG. XVII 2

Gray rabbit. Perfusion pressure i
case that supplied by Ciba) injecte
reserpine in 0 05 ml. of the same
arrow (McQueen, E. G., Doyle, A. E., and Smirk, F. H., Circulation, 11 : 161-169, 1955, by permission)

higher doses of reserpine are needed to inhibit the pressor reflex of the carotid sinus than when the brain stem is intact. Dasgupta et al. (1953) found a greatly augmented response to a solution of total alkaloids when given intracisternally rather than intravenously. Lim, Moffitt and Glass (1955) confirmed the observation that hypotension occurred after intraventricular injection of *Rauwolfia* alkaloids. We (McQueen, Doyle and Smirk, 1955) tried injecting reserpine intracisternally but found difficulty in obtaining consistent results because the solvents available to us were irritant and of themselves induced large changes in the blood pressure level. In other experiments, however, we found evidence of a central action [56, 60]. Thus, in rabbits with one ear sympathectomized the administration of reserpine gives rise to much greater dilatation of blood vessels in the innervated ear. As will be seen, there

is also a peripheral action. Further evidence of a central nervous action was obtained by Horwitz and Wang (1956) who found that the pressor response to electrical stimulation of the medulla was much reduced after administration of reserpine.

Evidence of a peripheral site of action. The evidence that in animals there is a peripheral as well as a central site of action for reserpine seems to be conclusive.

McQueen (1954) and McQueen, Doyle and Smirk (1954, 1955) showed that in grey rabbits dilatation of the innervated perfused hind limb occurred on injecting 0.015 mg. of reserpine intra-arterially, as was shown by a decrease in the perfusion pressure (Fig. XVII 2). The vehicle in which the reserpine was dissolved induced no such effect. It

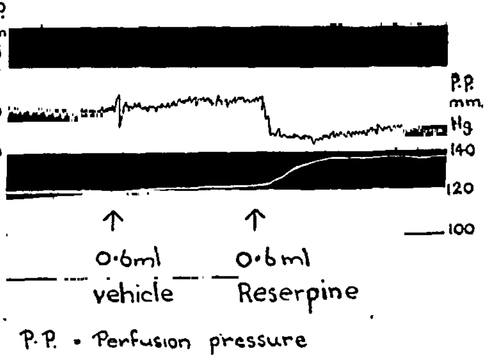
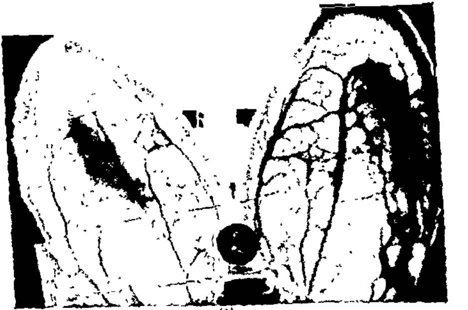



Fig. XVII 3

Gray rabbit, 1.5 Kg. Upper record, systemic blood pressure recorded via carotid artery. Manometer scale shown on left is mm Hg. Lower record perfusion pressure in isolated innervated hind-limb. Manometer scale on right. At arrows injection made into a cannula situated in an external jugular vein. Vehicle is that supplied by Ciba Ltd. for use as a solvent for reserpine. Six-tenths ml reserpine (in solvent) = 1.5 mg. (McQueen, E. G., Doyle, A. E., and Smirk, F. H., Circulation, 11 : 161-169, 1955, by permission).

is of interest that the peripheral action appears to have importance in causing the blood pressure falls in anaesthetized grey rabbits when reserpine is injected intravenously. When the rabbit hind limb circulation was isolated from the rest of the body and perfused with Gallagher's (1954) erythrocyte-dextran medium it was found that

injection of reserpine into the upper part of the body led to vasoconstriction in the perfused hind limb which was separated except for nervous connections. Evidently the fall of blood pressure in the



(a)



(b)

Fig XVII 4

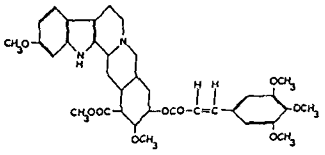
Rabbit ears (a) before reserpine, (b) after reserpine. The sympathectomized ear is on the right of the photograph (McQueen, E G, Doyle, A E, and Smirk, F. H' Circulation 11 161-169, 1955, by *permission*).

anaesthetized rabbit was due, at least in part, to a peripheral effect of the drug such that the nervous regulators reacted by attempted vasoconstriction. In the upper part of the body the peripheral action predominated, but in the perfused hind limb, where no drug was present, constriction of nervous origin predominated (Fig. XVII 3). In contrast when hexamethonium is injected into the upper part of a rabbit, and the lower limb is perfused, a decrease in the perfusion pressure is induced indicating vasodilatation. This, however, is not the case in the ear of the unanaesthetized rabbit because, where one ear is denervated and the other retains its innervation, the intravenous injection of reserpine causes more vasodilatation in the ear with an intact nervous supply (Fig. XVII 4).

Tripod and Meier (1954) demonstrated a peripheral action by showing that reserpine antagonized the vasoconstrictor actions of adrenaline, serotonin and barium chloride on the isolated rabbit leg. McQueen and Blackman (1955a) showed that in the isolated, pithed, perfused hindquarters of the rat, with the vascular tone enhanced by noradrenaline, pitressin or barium chloride, the addition of reserpine to the perfusion medium caused decreases in the perfusion pressure, which did not occur when the vehicle in which reserpine is dissolved was administered alone as a control.

### Rescinnamine (Rescamine)

Experiments in animals with rescinnamine indicate that its pharmacological effects and sites of action resemble those of reserpine. It has been shown by Cronheim et al. (1955) that it causes blood pressure reduction, sedation and relaxation of the nictitating membrane in dogs.




RESCINNAMINE

Its action is to produce a fall of blood pressure which may take a few hours to reach its trough, though an immediate fall of blood pressure, usually a small one, is sometimes present. Rescinnamine, like reserpine, reduces or abolishes the pressor responses to certain stimuli. The pressor response to bilateral occlusion of the carotid arteries is diminished in dogs, as is also the pressor response to stimulation of the central cut end of the vagus nerve. The pressor response to hypoxia is reversed (Cronheim et al., 1955). As with reserpine, the fall of blood pressure

from rescinnamine is associated with bradycardia. The doses of reserpine and rescinnamine required to produce a hypotensive action in [illegible] appear to be of the same order. The drug also in- [illegible] of 10 mg./kg. caused [illegible]

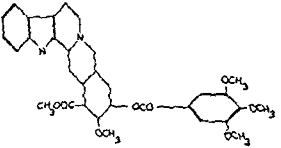
2 mg./kg.

McQueen and Blackman (1955 a, b) showed that, like reserpine, rescinnamine had a direct depressing action on blood vessels of the rat. The effect was seen in experiments where injection of rescinnamine [illegible] pithed hindquarters of the rat, in [illegible]

in the response to direct stimulation [illegible] interest that whereas reserpine appears to have an irreversible action upon this diaphragm preparation, the action of rescinnamine can be reduced by repeated washing of the preparation.

## Canescine

A potent alkaloid from *Rauwolfia canescens* Linn. was isolated by Klohs et al. which they referred to as "recanescine", and by Stoll and Hoffman (1955) who called it "canescine". Another report on its isolation came from Slater et al. (1955) and still another early description of the



CANESCINE

same alkaloid came from Schlittler et al. (1955) who called it "deserpidine". It seems likely that the substance will be called "canescine". Canescine is closely related chemically to reserpine and its constitution has been given as 11-desmethoxyreserpine by Slater *et al.* (1955), Cerletti et al. (1955) and by Schlittler *et al.* (1955).

In laboratory animals the effects of canescine resemble those o[f] reserpine very closely. This is stressed by Slater et al. (1955) who d[id] not discover any pharmacological differences between the two alka[loids]

loids. Cronheim et al. (1955) Packman et al. (1956) and Schneider et al. (1955) make a corresponding observation and Cerletti et al. (1955) also state that the two alkaloids, reserpine and canescine, are practically indistinguishable. It is of great interest that (1) certain changes in the molecule of reserpine can be effected without loss of its properties and (2) that despite the great similarity of the effects of canescine and reserpine in animals there is no difficulty at all in distinguishing between the actions of these substances in man.

Blood pressure falls were noted in the cat by Slater et al. (1955), Cerletti et al. (1955) and McQueen (unpublished observations), and in dogs by Cronheim et al. (1955). After intravenous administration there was sometimes a small, prompt fall of the blood pressure but the main fall took an hour or several hours to develop [18, 92].

Certain pressor reflexes are diminished by canescine such as (1) the pressor effect from bilateral carotid artery occlusion [18, 55, 92], (2) the pressor response to central vagal stimulation [18, 55, 92].

The effects on pressor reflexes did not usually appear immediately but might require 3 to 6 hours for the effect of an intravenous injection of canescine to develop. There was no diminution in the pressor response to adrenaline [12, 18, 92]; in fact, more often the pressor action of adrenaline was increased. Usually the heart rate was diminished [12, 18].

McQueen and Blackman (1955a and b) have shown that recanescine has also a direct vasodilating effect in the perfused, innervated, but otherwise isolated, hind limb of the rabbit; and in the perfused hind quarters of the rat in which the vasomotor tone has been increased by infusion of noradrenaline, pitressin or barium chloride. The duration of the effect of canescine appeared to be somewhat less than that of reserpine, and rescinnamine seemed to lie intermediate between the two.

McQueen and Blackman (1955a) studied the duration of effect of these three alkaloids by means of the innervated rat diaphragm preparation (Bülbring, 1946). They found that 1 mg of alkaloid in a 50ml. organ bath caused progressive diminution in the magnitude of the contractions elicited by nervous stimulation, and a smaller impairment of the contractions elicited by direct stimulation of the muscle With reserpine the effect of the inhibition of nervous stimulation could not be removed by repeated changing of the immersion fluid, whereas in the case of canescine and rescinnamine, some degree of recovery of function after washing was observed. The suggestion was made that the rescinnamine and canescine which are rather more soluble than reserpine may be able to enter and leave cells more readily.

There are actions on the central nervous system which resemble those of reserpine. Cerletti et al. (1955) were unable to distinguish between the sedative effects of canescine and reserpine in mice and dogs. Slater et al. (1955) studied the effect on aggressive behaviour in

rhesus monkeys and it was found that 1 mg./kg. of recanescine had the same remarkable effect as reserpine, the animals becoming docile and easy to handle. Miosis occurs with canescine as with reserpine in mice (Cerletti et al., 1955), rabbits (Slater et al., 1955), dogs (Cerletti et al., 1955; Cronheim et al., 1955) and monkeys (Slater et al., 1955). There is relaxation of the nictitating membrane in dogs (Cronheim et al., 1955), and ptosis in mice and rabbits (Slater et al., 1955). Such actions can be interpreted as effects, direct or indirect, upon the hypothalamus.

## Serotonin Release by Certain Rauwolfia Alkaloids

A fascinating chapter of medicine opens with the discovery that the administration of reserpine leads to the release of serotonin from the brain and other organs. Pletscher et al. (1956b) found that rabbits given 5 mg. per kg. of reserpine and killed after 16 hours had lost 90 per cent of brain serotonin. A decrease of 75 per cent occurred in 30 minutes. They found that serotonin was in much greater concentration in the brain stem than in other parts. Pletscher et al. (1956a) find that [illegible] alkaloids such as rescinnamine and canescine cause [illegible]

[illegible] nence. Paasonen and Vogt (1956) however, found some decrease in serotonin occurred after the administration of large doses of amphetamine.

Kuntzman et al. (1956) make the interesting suggestion that reserpine affects the brain sites responsible for binding serotonin. They find when the precursor of serotonin, 5-hydroxytryptophan, is administered, there is normally a marked increase in brain serotonin in [illegible] fails to take place in [illegible]

[illegible] no longer detectable in the brain, and their duration corresponds more [illegible]

[illegible] tonin from platelets in man and from the brain in rabbits following prolonged administration of small doses. Shore et al (1956) showed that reserpine liberated serotonin from platelets in rabbits, rats and guinea pigs. There was no platelet disruption and loss of over 90 per cent of serotonin had no significant action on the bleeding time. Bhattacharya and Lewis (1956) and Parratt and West (1956) have produced evidence that, at least in rat skin, much of the 5-hydroxytryptamine is held in tissue mast cells

Bogdanski and Udenfriend (1956) have determined the distribution of serotonin in fresh brain tissue and find the following figures (in

μg. per gm.) in dog and cat brain respectively: medulla 0.55, 0.53; pons 0.41, 0.33; cerebellum 0.07, 0.30; midbrain 0.97, 1.23; thalamus 0.65, 0.78; *hypothalamus* 1.75, 1.75; olfactory bulb (dog) 0.38; brain gyri 0.17, 0.24; white matter 0.07; cortical grey matter 0.34. Serotonin is a substrate of monoamine oxidase and it is of interest that the following amounts of added serotonin (in μg.) were destroyed per gm. of homogenized dog brain tissue per hour: medulla 1,250; pons 882; cerebellum 970; midbrain 903; *hypothalamus* 3,164; thalamus 886; cortex 844. Such a result suggests that serotonin plays an important part in hypothalamic activity and gives additional support for a hypothalamic site of action for reserpine.

When 5-hydroxytryptophan is administered in doses sufficient to raise the serotonin content of the brain considerably, excitatory responses occur which are rather similar to those induced by the administration of the hallucinogen, lysergic acid diethylamide. Brodie et al. (1956) find that similar effects are induced by the administration of reserpine to rabbits pretreated with iproniazid (marsilid), an amine oxidase inhibitor. Chessin et al. (1956) also found that after pretreatment with iproniazid, dogs responded to reserpine by blood pressure elevation, contraction of the nictitating membrane, tachycardia and hyperpnoea. Irponiazid inhibits monoamine oxidase which rapidly destroys serotonin.

Erspamer (1956a) finds the concentration of serotonin is higher in the platelets than in the brain and gastrointestinal tract and that it is released by reserpine. The serotonin is apparently broken down after release into 5-hydroxyindolacetic acid, which appears in the urine. After reserpine administration there is an increase of the urinary excretion of 5-hydroxyindolacetic acid. When 5-hydroxytryptophan is given subcutaneously to the rat about 27 to 46 per cent appears in the urine in the form of 5-hydroxyindolacetic acid (Erspamer, 1956b).

Schneider and Rinehart (1956) found that 1.0 mg. per kg. of reserpine augmented the pressor response to serotonin in dogs. Ganglionic blockade also caused augmentation. In spinal dogs with bilateral vagotomy the pressor action of serotonin was antagonized by reserpine. The authors conclude that reserpine causes central potentiation combined with peripheral antagonism. The interesting question arises, whether the nervous system effects are the result of serotonin depletion from brain cells or whether they are due to the presence of free serotonin.

Evidence that the action of reserpine may be brought about by the presence of free serotonin is that dogs pretreated with reserpine are reported to have a profound fall of blood pressure following the intravenous infusion of serotonin (Cronheim and Gourzis, 1956).

Apparently in contrast, B.A.S. (1-benzyl-2,5-dimethyl serotonin HCl) has been reported by Woolley and Shaw (1956) to be an antiserotonin, and Wilkins (1956) finds that it has actions in man resemb-

ling those of reserpine including a definite though mild hypotensive action.

## Other Alkaloids of Rauwolfia Exhibiting Hypotensive Activity

*Serpe*

Ser
Siddiq
cause
of 10
two spinal cats (Chopra and ...
reversed after the administration of ergotoxin and a blood pressure rise ...
(Chopra et al, 1942). De Jongh and Proosdij-Hartzema (1955) noted a fall of
bloo ... higher blood pressure was maintained by
adre
cons
ed by serpentine in a ... in the dog the intestines also ex-
]
]

sider that its hypotensive action is mainly at a ...

*Iso-ajmaline and neo-ajmaline*

Iso-ajmaline and neo-ajmaline were isolated by Siddiqui and Siddiqui (1939) from the roots of *Rauwolfia serpentina* grown in the Dehra Dun district but not from the Bihar variety.

These substances lower the blood pressure in spinal and decerebrate animals and depress the cardiac and intestinal muscle. The nervous system is first stimulated and later depressed. There is a pharmacological difference between the two substances: iso-ajmaline causes mild depression of the uterus in guinea-pigs and cats, whereas, neo-ajmaline causes strong stimulation.

*Serpine*

Serpine (Chatterjee and Bose, 1954) causes a marked but brief fall of blood pressure and has been considered to have a sympathicolytic action similar to that of yohimbine

*Rauwolscine*

and decreases its action on the heart. A fall of blood pressure has been noted also after intraperitoneal injection of monkeys and in cats (Das et al, 1955). The intracisternal administration causes vasodilatation without much change in the cardiac output, suggesting a central point of action (Das et al, 1955).

## Alkaloids of Rauwolfia Reputed to Have an Indecisive or no Hypotensive Action

*Ajmaline*

Ajmaline was isolated from *Rauwolfia serpentina* by Siddiqui and Siddiqui (1931). The substance does not have uniform effects upon the blood pressure.

In two decerebrate cats the blood pressure was raised and in two spinal cats it was lowered (Chopra and Chakravarti, 1941; Chopra et al., 1942). Where the blood pressure has been first raised by *adrenaline* or ephedrine, then the injection of ajmaline causes a blood pressure fall (Raymond-Hamet, 1936; Chopra et al., 1942). Bhargava and Borison (1956) also find variable effects from ajmaline (2—5 mg./kg., I.V.) on the blood pressure of the cat. The pressor action is [illegible] A heavy dose of ajmaline (50 mg). in cats [illegible] ion of adrenaline[14]. The isolated intestine of [illegible] increased peristalsis when exposed to con- [illegible][14]. The substance is not sedative, it causes medullary stimulation and may provoke convulsions[14].

### *Serpentinine*

Serpentinine is a yellow alkaloid isolated from *Rauwolfia serpentina* by Siddiqui and Siddiqui (1931). This substance raised the blood pressure in decerebrate cats (Chopra and Chakravarti, 1941, Chopra et al., 1942), lowered it in one spinal cat and raised it in another spinal cat (Chopra and Chakravarti, 1941). If the blood pressure is first raised by the administration of adrenaline or ephedrine, then serpentinine causes a fall of blood pressure[14] The direct action of serpentinine on the blood pressure is almost unaffected by ergotoxin[14]. The isolated heart of the kitten was stimulated by serpentinine in concentrations of 1/200,000, but the cat's heart *in situ* was depressed[14]. It caused contraction of the isolated guinea-pig intestine[14]. The alkaloid is said to be slightly sedative in mice[14] but in most animals it is not sedative, but causes medullary stimulation and may provoke convulsions[14].

### *Yohimbine*

Yohimbine is present in *Rauwolfia serpentina* It has an adrenolytic, and to a lesser extent, a sympatholytic action. Large doses may reverse the action of adrenaline. Intravenous injection may elevate the blood pressure but it is stated (Mercier and Delphaut, 1936) that intraspinal or sub-occipital injection lowers the blood pressure and induces anaesthesia. Skin vasodilatation may be induced. The alleged aphrodisiac action is probably lacking. It was suggested at one time for the treatment of hypertension, but according to Lawrence (1912) a further rise of blood pressure may occur as the result of its administration.

### *Other substances derived from rauwolfia*

Little definite is known about the remaining substances from Rauwolfia, namely, raupine[4], reserpinine[14], [19], alloyohimbine, sarpagin[101], chalchupina A[11], chalchupina B[12], alstonin[13], and rauwoline[18]

## Clinical Studies with Mixed Rauwolfia Alkaloids and Reserpine

Reserpine is generally regarded as responsible for much of the pharmacological activity of the Rauwolfia genus and most early reports on this subject suggest that the effects of preparations of whole root, total Rauwolfia alkaloids, the alseroxylon fraction and of reserpine, are almost indistinguishable except for the magnitude of the effective dose. Evidence is emerging that some other Rauwolfia alkaloids have effects which can be distinguished from those of reserpine and which

are lik[illegible] [illegible] and clinical importance. For this reason [illegible] and reference [illegible]. It may be assumed, however, that in equally hypotensive doses there are few differences between the mixed alkaloidal preparations and reserpine.

## Oral and Parenteral Dosage

Reserpine may be administered parenterally or orally and despite its low solubility, absorption appears to be good, at least of moderate doses. Doses ranging from 0.5 to 10 mg. have been given parenterally, even intravenously, in the course of investigation on hypertensive patients, for the treatment of hypertensive crises and in psychiatric clinics for the initiation of treatment. With doses such as 0.75 to 1 mg. of reserpine daily the hypotensive action may be evident in a week and may [illegible] weeks after withdrawal of the drug[109]. Originally [illegible] satisfactory dosage [illegible] 0 5 mg. daily[26, 27, 93]. Wilkins (1954a) usually starts with 0.1 mg. four times daily but may reduce this at a later stage. Such large doses of reserpine as 5 to 10 mg. daily, used in the treatment of psychoses may induce large falls of blood pressure in normotensives to such levels as 60/50, 64/46 mm. Hg[30]. See also page 542.

## Drug Toleration

There is fairly general agreement that the administration of Rauwolfia alkaloids even for years does not lead to drug toleration in respect of the hypotensive action[112]. This is our experience also. It is sometimes stated that with continued administration, toleration develops to the side effects We have not observed this to any extent, and have seen at least one important side effect, mental depression, develop even after a year of successful treatment. It is well to recognize also that, with repeated administration of reserpine, a degree of cumulation occurs, so that the full effects may not be evident for several weeks.

## Hypotensive Action

Even after intravenous injection of 3 to 6 mg. doses, the time taken for the blood pressure fall to reach its trough may be 1½ up to even 6 hours[28, 32, 38, 105]. In our experience the maximum fall of blood pressure from large doses is preceded, in man, by considerable flushing and somnolence The trough of the blood pressure fall usually occurs over an hour later, at a time when sedation is less pronounced and facial flushing has disappeared[28]. The blood pressure falls after oral administration of large doses, such as 6 or 9 mg. (Fig. XVII 5), usually occur about 4 to 8 hours after administration and exceed the falls

encountered with placebos [28, 30]. Appreciable falls are also encountered in normotensive persons on large doses of reserpine [9]. Such large doses are unsuitable for routine administration in hypertension. With 1.5mg.

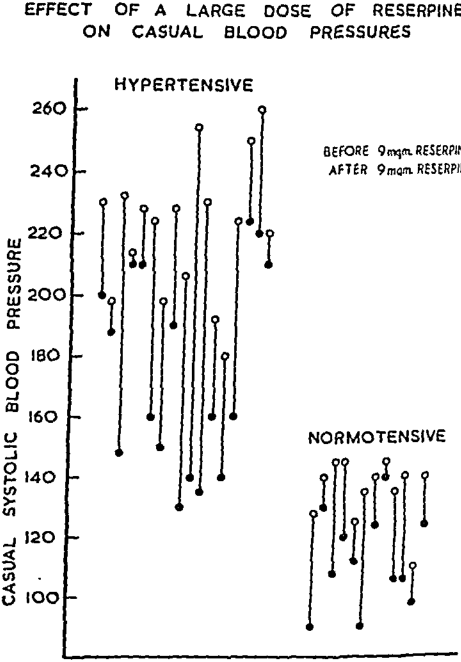



Fig. XVII 5

Effect of large doses of reserpine on the casual systolic blood pressures of 17 hypertensive and 12 normotensive persons Circles indicate the blood pressures before and dots the blood pressures after administration.

of reserpine daily, a full effect may be seen within two weeks, but with such small doses as 0.25 to 0.5 mg. daily the full extent of the

blood pressure fall may be delayed for six weeks or more. Some of the falls in casual blood pressure which take place when the patients are ... of emotional tension in the clinic

patients are more likely to respond to reserpine ... most remedies) than are the severe cases with high diastolic blood pressures.

Wilkins (1954a) and Wil... pressures of patients on pla... with reserpine, found the averages of the ... from 191/109 to 167/94. In more severe cases Wilkins usually found it necessary to combine the administration of reserpine with some other drug, such as hydralazine, a veratrum alkaloid, or hexamethonium. Our experience was very similar; in severe cases an adequate blood pressure reduction with reserpine alone occurred in a minority of patients, even with 0.5 to 1.5 mg. daily. In many advanced cases there was no fall of blood pressure, but sometimes patients with severe "fixed" hypertension would exhibit falls to well below the basal blood

... occurrence of a paradoxical *hypertension* on reserpine treatment were reported by Tyhurst and Richman (1955) who were using 8 mg. daily in psychiatric cases.

Patients on reserpine show much less liability to fluctuations of the casual blood pressure. The greater stability of the blood pressure is seen also when reserpine is combined with hexamethonium or pentolinium [26, 27, 65]. Usually blood pressure falls last for one or two weeks

test is not greatly influenced, though ... rises were slightly increased.

## Orthostatic Hypotension

The doses of reserpine ordinarily used in the treatment of hypertension (1.5 mg. or less daily) do not cause orthostatic hypotension [28, 115] and even larger doses often fail to do so [28]; but, when large doses of 5 to 10 mg. per day are employed, as in psychiatric treatments, orthostatic hypotension may be encountered [7, 42, 81, 240].

## Cerebral Circulation

Hafkenschiel et al. (1955) studied the cerebral circulation after doses of 2.5 to 5.5 mg. in patients with moderate and severe hypertension. They found, approximately, a 20 per cent reduction in the arterial

pressure, and the cerebral vascular resistance was reduced, but the cerebral blood flow and the venous oxygen tension were unchanged after the reserpine; also the uptake of glucose was unchanged.

## Renal Circulation

Hughes et al. (1954) found no important change in the renal circulation of hypertensive patients after reserpine. A slight decrease in the glomerular filtration rate occurred at the trough of the blood pressure fall after intravenous injections. Krogsgaard (1956) found little change in creatinine and para-amino hippuric acid clearances but noted a fall in urine output and sodium excretion following large intravenous injections.

## Effect on Heart Rate and Heart Output

Reserpine causes a decrease in the heart rate [41, 42, 109, 112, 113], often of about 10 beats per minute. Electrocardiographic and other evidence indicates that the bradycardia is of sinus origin, and that it can be antagonized by the administration of atropine. Bixby (1955) reported six cases in which attacks of paroxysmal auricular tachycardia were prevented by reserpine in doses of 0.25 mg. up to four times daily.

Rea and Fazekas (1955) reported a death after the parenteral administration of a large dose of reserpine. The patient showed the syndrome polyfocal premature ventricular systoles with the appearance of R waves on T waves (Smirk, 1949), which is often an ominous sign. Reference to the subject of fluid retention and "heart failure" is made under the heading of "metabolic and endocrine effects".

## Effect of Reserpine on the Central Nervous System

The effects of reserpine upon the higher centres of the nervous system have found an important use in psychiatry; they may be advantageous or sometimes disadvantageous to hypertensive patients.

In favourable cases doses of reserpine up to 0.5 mg. daily, and sometimes even up to 1.5 daily, induce a state of quietude, restfulness and decrease of anxiety without undesirable side effects, and prove of great help to tense or overanxious hypertensive patients. Such doses sometimes induce drowsiness but they do not necessarily promote sleep, and indeed patients may be sleepy during the day and have less sleep at night. Very large doses, such as 5 or 10 mg. daily, for psychiatric cases do not lead to deep sleep, though they cause drowsiness, and patients can be aroused readily and are usually capable of an intelligent response. The electroencephalograms of patients who have been rendered drowsy by the drug still exhibit the characteristics of a wakeful state [24, 37, 66].

Although many of the important benefits of reserpine arise from

their action on the higher nervous centres, so also do the most important side effects. Occasionally patients show mild degrees of euphoria which are due partly to the direct action of the drug and partly to relief from hypertensive manifestations. While many patients are conscious of a welcome tranquility and decrease or disappearance of tenseness and anxiety; others, especially on doses exceeding 0.5 mg. daily, remark on their lethargy, decrease of initiative and unaccustomed laziness. Such patients may be either comfortable and indeed pleased with their change in disposition; others, especially men in responsible positions, are impatient and disturbed by their indolence and loss of drive, and regard their mental changes as an unwelcome side effect. Drowsiness is one of the commonest side effects [27, 41, 109, 111, 113]; it may be combated to some extent by amphetamine 5 or 10 mg. administered in the morning. Nightmares or excessive dreaming are not uncommon [35a 42, 100a 105, 109, 113, 115]. The dreams which may be peculiar and vivid have been described aptly by Smith (1955) as "Salvador Dali dreams".

Some patients tell us their dreams are vivid and strange, other patients report that there is nothing unusual about them. Some reserpine dreams are pleasant, some unpleasant and some erotic.

Such nervous manifestations, while requiring adjustments of the régime, have seldom been a cause for anxiety, but the occurrence in some patients of serious degrees of mental depression has led to grave distress and has caused more concern to us in the care of our patients than any other feature of hypotensive therapy. In some instances definite depressions have only been revealed on direct enquiry, the possible relationship to reserpine being unrecognized by the patient. We have encountered also several instances in which depression was evidently psychotic, requiring a reference to a psychiatric physician and in some patients admission to a mental hospital. Several such cases have occurred also in the practices of my colleagues.

In milder cases the withdrawal of reserpine has been followed within a few weeks by lifting of the depression, in other instances it has persisted for several months. In the more severe cases electrical convulsive therapy seems to have accelerated recovery considerably. Burrell (1956) reported similar experiences. Apparent recovery in some patients was followed by a recurrence within a week or so of returning home, but in all of these so far, with one potential exception, there has been eventual recovery.

When the occurrence of this side effect of reserpine was recognized [29, 31] we turned to the records of these patients and found that several of them had experienced a substantial depressive illness in the past, including in some instances an admission to a mental hospital. Some patients, however, had exhibited no indication of a predisposition. Other reports of depression come from Wilkins (1954 a, b), Freis (1954)

MacArthur and Isaacs (1955), Smirk and McQueen (1955b), Wallace (1955), Achor et al., (1955), Muller et al. (1955), Schroeder and Perry (1955), Lemieux et al., (1956) and Tweedy (1955). Locket (1955) treated 39 severe hypertensive patients and depression occurred in five, one of them attempting suicide. Depressions have been reported also in the treatment of non-hypertensive patients with psychotic or psychoneurotic disorders. We have had one suicide and two attempted suicides in 250 patients; Platt and Sears (1956) had one suicide in 64 patients.

There is little doubt that when reserpine is administered to patients in the more disturbed wards of mental hospitals the incidence of assault, of noisy and unco-operative behaviour are appreciably less and [illegible] [illegible] phrenia and aggressive behaviour and for states of manic excitement, tenseness and anxiety. Several writers indicate that they have had less help or no improvement in depressed patients and where depression was one of a number of complaints the depression did not improve. It is of interest that Sen and Bose (1931) said that Rauwolfia was effective only in certain types of insanity, namely those with maniacal symptoms, and was contraindicated in insanity of a morose type. Davies and Shepperd (1955) reported no benefit in depressed patients. Although in the course of treatment of psychotic patients the occurrence of depression as a complication of reserpine administration is referred to,[82, 83a] it is remarkable that this complication has not been reported more frequently in mental hospital practice. Morgan (1956) has encountered depression developing in the course of mental hospital treatment with large doses of reserpine. He remarks on the severe reactions which may recur with convulsive therapy — presumably in patients on large doses.

A much less common and less important symptom than mental depression is restlessness, tenseness or agitation (Tuchman, Sletten and Crumpton, 1954; Corcoran et al., 1954, Doyle, McQueen and Smirk, 1955; Kert et al., 1955; MacArthur and Isaacs, 1955; Moore and Martin, 1955). In our experience it has been relieved readily by omission of the drug.

Another important nervous system side effect is the development of Parkinsonism, which occurs principally with the large doses used in psychiatric treatment [2, 21, 43, 82, 100]. Parkinsonism appears to be uncommon with the small doses, under 1 mg. daily, in use for hypertension. Patients with this complaint have improved within a week or so of discontinuing therapy (Shuman, 1955; Richman and Tyhurst, 1955).

The continued administration of reserpine does not lead to addiction nor are there withdrawal symptoms when the drug is omitted.

The drug Ritalin has been recommended as an antagonist to inert

and depressed states which may develop during reserpine treatment. Cole and Glees (1956) found a striking relief of reserpine apathy and inertia in macaca monkeys who were given Ritalin. Feinblatt et al., (1956) also obtained relief from inert states by the thrice daily administration of 8 mg. of ephedrine.

*Comment on the central nervous system action.* — I have been impressed by the fact that, with the exception of the more substantial depressions, the side effects of reserpine clear rapidly when the administration is discontinued. Even Parkinsonism, involving a profound nervous disturbance is reported to clear within two weeks. The more severe depressions, however, have not lifted rapidly with the withdrawal of reserpine; they have usually continued for one or two months, sometimes for three or four. One possible explanation is that the drug does not induce depression directly but, under the action of reserpine the operations of the mind have changed, so that a depressive state may be built up, the continuance of which does not depend on drug action. Some support for this hypothesis comes from the observation of serotonin depletion from brain tissue, which persists after the reserpine has been eliminated. As already mentioned, several of our patients with severe depression had had episodes of depression before undertaking reserpine treatment. Some other patients on reserpine who had no antecedent history have experienced depression in relation to a shock or bereavement. The study of reserpine-induced depressions may be a means of advancing our knowledge of the origin of states of depression.

### Metabolic and Endocrine effects

The occurrence of drowsiness, lassitude and bradycardia led to some studies of the endocrine function. The question of whether the basal metabolic rate is reduced by reserpine was studied by Hughes et al. (1954) who found it substantially unchanged, and the radio-active iodine uptake by the thyroid gland was not altered by the administration of Rauwiloid. Probably these results apply also to reserpine. Winsor (1954) noted that the administration of reserpine does not influence the eosinophile count and he did not find evidence of any

gain (Hughes et al., 1954; Wilkins, 1954b; Doyle, McQueen and Smirk, 1955; Tyhurst and Richman, 1955; McGregor and Segel, 1955, Marley and Pare, 1956). These actions are commonly attributed to an effect upon the hypothalamus. A little oedema is a common manifestation and probably salt retention is the explanation. Perera (1954), using *Raudixin*, recorded two cases of this in his series.

Cahn (1955) noted gross facial and leg oedema in a psychiatric case on large doses of reserpine. In several instances we have noted increase of breathlessness and oedema in heart failure patients who have had reserpine added to the régime. This we have also attributed to salt retention. In almost all such cases withdrawal of reserpine has been beneficial.

## Autonomic Side Effects

Several side effects are probably due to sympathetic inhibition. Nasal blockade is one of the most frequent minor discomforts [27, 30, 41, 42, 109, 113, 115]. Facial flushing may occur [27, 105].

Sympathetic vasodilatation may be at least partly responsible for a disturbance in temperature regulation. The body temperature may be one or two degrees below normal, and attacks of shivering and an increased susceptibility to cold is frequently encountered (Doyle, McQueen and Smirk, 1955). Warm clothes and well heated rooms seem to be necessary for the comfort of these patients.

Compensatory overactivity of the parasympathetic system seems to explain certain side effects such as vomiting which occurs occasionally (Hensler, 1953; Vakil, 1954), particularly after intravenous injection (Hughes et al., 1954; Smirk, unpublished observations). An increase in the frequency of bowel motions, leading occasionally to diarrhoea (Hoobler, 1954; Wilkins, 1954b; Winsor, 1954; Vakil, 1954; Doyle, McQueen and Smirk, 1955) is also a parasympathetic effect, as is the increased secretion of gastric juice (Hughes et al, 1954) which may lead to the activation of peptic ulcers (Putz and Spies, 1954; Kert et al., 1955). Cummins and Balfour (1955) report, however, that they found no increase in uropepsin excretion in 12 patients after administration of Rauwolfia alkaloids. The renal excretion of uropepsin is closely related to the secretion of pepsin in the gastric juice. Other evidences of autonomic imbalance are the occurence of bronchospasm (Vakil, 1954; Doyle, McQueen and Smirk, 1955), and biliary colic (Doyle, McQueen and Smirk, 1955). Although moderate doses of reserpine do not cause miosis in man, it may occur when the doses are large (Jeri, 1955). Decrease of libido (Wilkins, 1954a) is not uncommon in men and impotence has been described (Hughes et al., 1954) but is uncommon on reserpine alone. The sympathetic and parasympathetic innervation may both be involved in the production of this symptom. An increase in bladder tension following reserpine administration was reported by Maxwell et al., (1956).

The use of large doses of reserpine in the treatment of psychiatric disorders seems to have shown that there is little risk to bodily health from its administration. Intravenous injection may be associated with great fall of blood pressure and, rarely, collapse. Vakil (1954), however,

has encountered two cases of collapse on oral administration associated with allergic manifestations. A death from circulatory collapse has been reported following the intravenous administration of 10 mg. of reserpine (Rea and Fazekas, 1955). A 2 year old child survived a dose of at least 3 mg. of reserpine (Kayser, 1956).

## Clinical Studies with Rescinnamine (Rescamine)

When administered in man (Smirk and McQueen, 1955a, b) the [illegible] was found to be of the same order [illegible] administration [illegible] rescinnamine in hypertensive patients [illegible] with less diurn[illegible] and, as a rule, [illegible] usually less with rescinnamine than with reserpine [illegible] stances there is a definite anorexia.

We[86, 87] found that of 37 patients who had developed a mild or moderate degree of mental depression during treatment with reserpine, about 24 were improved on transferring to rescinnamine and most of them have been able to continue with rescinnamine for several months, and some for over a year, without recurrence of the symptom. Our impression has been that rescinnamine is less likely to induce mental depression than is reserpine, but 6 patients out of about 50 who have been treated with rescinnamine developed mental depression.

Rescinnamine resembles reserpine in having a somewhat flat dose-response curve. Nevertheless, in man, the difference between the effects of 0.75 mg daily and 1.5 mg. daily is usually associated with a difference in the blood pressure level and in the incidence of side effects.

The effect of 0 75 mg. daily of rescinnamine is roughly equivalent to that of 0 5 mg. of reserpine daily. Such doses are suitable also for combinations with ganglion blockers, and rescinnamine resembles reserpine in that it decreases the requisite doses of hexamethonium, pentolinium or SU 3088. The addition to a methonium régime of rescinnamine in a dose of 0 75 mg daily usually makes it possible to reduce the dose of the ganglion blocking agent used by one-third, or exceptionally by one-half, without loss and usually with improvement in the degree of hypotensive activity

The interim view of our clinic is that the dose of rescinnamine in hypertension should not exceed 1 mg. daily and preferably should not exceed 0 75 mg daily; but our experience of the last twelve months suggests that the incidence of mental depression is low if the dose of reserpine does not exceed 0 5 mg , or of rescinnamine 0.75 mg., daily.

Hershberger et al. (1956) gave doses of 10 mg. of rescinnamine intramuscularly or intravenously to 20 patients and noted falls of 20 mm.

of more in the mean blood pressure in 18 of them. They thought side effects were rather less than with reserpine.

*Comment on the differences between rescinnamine and reserpine.* — Rescinnamine and reserpine resemble each other so closely in animal experiments that it has been stated that no distinction can be made between them: this is certainly not the case in man. While some patients cannot distinguish between the two substances, others feel subjectively different and there appears to be good evidence that diurnal drowsiness and weight gain are less with rescinnamine and that some patients who have had appreciable mental depression with reserpine can tolerate rescinnamine. Rescinnamine is not preferable to reserpine in all patients. The difference between the two drugs seems to depend mainly on differences in their actions on the higher centres of the nervous system. This no doubt explains why the responses of patients are highly individual, as for example in the tendency to cause dreaming.

## Clinical Studies with Canescine

Our clinical experience with canescine [61] suggests that its hypotensive action is similar to that of reserpine but that the requisite dose is about 2 to 2.5 times as large. When administered alone falls of blood pressure are sometimes considerable but ordinarily are small and not distinguishable in all cases from the effects of placebos. With moderate doses (say 1 mg. daily) a fall of blood pressure may not be established for several weeks. If large doses, say 4 mg., are administered, then some fall of blood pressure may be apparent on the day of administration. There is no doubt that in order to obtain equal hypotensive actions with the two substances, canescine must be given in at least double the dose of reserpine, and at such doses the sedative action of canescine appears to be less than that of reserpine. When the drugs are given in equi-hypotensive doses, many patients are unable to distinguish subjectively between canescine, rescinnamine and reserpine. Others are convinced that there are differences in the prominence of the side effects such as swelling of the nasal mucous membrane, dreaming and others already referred to in the section on reserpine.

Canescine shares with reserpine and rescinnamine the property of enhancing the response to ganglion blocking agents, and this action is demonstrable in all or practically all patients An adequate hypotensive action can be induced with a [illegible] thus reducing side effects. In [illegible] pressure induced by ganglion [illegible] and casual blood pressures are less deceptive as a guide to dosage control.

In several of our patients who developed mental depression on reserpine, a change to canescine was eventually associated with lifting

of the depression. Experience with this substance is far too short to enable us to say that the incidence of depression is much less than with ... doses of reserpine or rescinnamine, but the im- ... that ... to be ... more satisfactory than reserpine or rescinnamine ... f the incidence of side effects. Of 11 patients who had had depression on reserpine 3 continued to have depression on canescine and 8 improved. In all 27 patients had a trial on canescine and one developed a mild depression.

## TREATMENT OF HYPERTENSION BY RAUWOLFIA ALKALOIDS

Decisions concerning hypotensive therapy with the Rauwolfia alkaloids should take account of the following observations:

... weeks of treatment.

2 Reserpine and other Rauwolfia alkaloids are not innocuous substances as some of them at least may cause psychotic depression. Apart from the risk of this complication, they are suitable for long term administration.

A definite risk of depression is present with reserpine in daily doses of 1.0 mg; it is present but appears to be less with rescinnamine in daily doses of 1.5 mg; it is probably still less with canescine in daily doses of 1 5 mg The risk of depression is present with whole root and with *preparations* containing mixed Rauwolfia alkaloids, but *for an* equal hypotensive action is probably somewhat less than with reserpine

3 The active Rauwolfia alkaloids when used in combination with ganglion blocking agents may be relied upon to supplement or potentiate their hypotensive action in almost all patients.

### Dosage of Rauwolfia Alkaloids

The technique of using *Rauwolfia alkaloids* in the treatment of ... d ... e ... t. Although there is a *flat dose-response curve* there are recognizable differences in the degree of blood pressure reduction with different ... of mental depression with higher doses. Suggested doses are:

JJ

| | |
|---|---|
| Reserpine | 0.25 to 0.50 mg. |
| | (exceptionally 0.1 mg. daily is effective) |
| Rescinnamine | 0.50 to 0.75 mg. |
| Canescine | 0.50 to 1.00 mg. |
| Alseroxylon fraction | 4.00 to 8.00 mg. |
| Whole root preparations | 200 to 400 mg. |

These are ordinarily the doses we now employ and with over 200 patients on Rauwolfia alkaloids we have had no serious case of depression in twelve months. Previously, on larger doses, we had several severe depressions.

### Use of Rauwolfia Alkaloids as Sole Hypotensive Agents in Mild or Labile Hypertensive Patients

The question of whether mild cases of hypertension should be treated with Rauwolfia alkaloids will be answered better when we know the incidence of severe depression in patients on various doses of Rauwolfia alkaloids. Probably on the recommended doses the incidence of depression is low enough to warrant the use of Rauwolfia alkaloids in mild cases, provided this is justified by an adequate effect on the blood pressure.

In comparatively mild or labile cases of hypertension under consideration for long term treatment with Rauwolfia alkaloids, it seems desirable to compare their action with a placebo, or perhaps better with phenobarbitone, in order to decide whether any effect obtained during Rauwolfia administration could be obtained also by simple measures, such as reassurance and phenobarbitone.

There is ample evidence that in some patients the hypotensive action of Rauwolfia alkaloids greatly exceeds that of placebos or phenobarbitone, but not all patients respond. Unresponding patients should not be exposed to the disadvantages of the drug.

The steps, therefore, to be taken would appear to be:

1. A careful history as regards previous incidence of depression.
2. A clinical trial of one month phenobarbitone (½ gr. twice daily) or alternatively a placebo, two months on a Rauwolfia preparation at a low dosage level (0.25 mg. reserpine twice daily), and after two months, return for two months to phenobarbitone and then back again to the Rauwolfia preparation if it has proved itself effective.
3. Casual blood pressures taken weekly usually provide an adequate degree of supervision for a Rauwolfia régime during the trial period, and a monthly or two-monthly visit thereafter.

## Use of Rauwolfia Alkaloids as Sole Hypotensive Agents in Severe Hypertensive Patients

In severe hypertensive patients the results with various Rauwolfia [illegible]

[illegible] delay in the treatment when patients are in a hypertensive crisis or when the patient's condition is evidently deteriorating. Disappointment with the r[illegible] in severe cases is widespread.

Vakil (1954) [illegible] nephrosclerosis, [illegible] although he obtained some relief in subjective manifestations, he observed only minor changes in the objective findings. Stappenbeck (1954) and Meyer-Leddin (1954) had better results with Rauwolfia alkaloids in mild than in severe hypertensive patients. In patients with hypertensive heart failure Hughes et al. (1954) had improvement in only one out of five cases treated for periods of two to seven months. This contrasts with the very high rate of improvement in hypertensive heart failure when ganglion blocking agents are used effectively. *Hughes et al.* found decreases in heart size in only one of 31 cases, improved E.C.G. in 6 out of 28 cases, and improvement of the fundi in 0 of 8 cases Blood pressure levels, however, were improved to some extent in 24 out of 47 cases and headaches in 14 out of 15 cases.

Locket (1955) treated 39 severe hypertensive patients for six to twenty months with Rauwiloid He used 1000 mg. doses daily of whole root or, alternatively, 8 mg. daily of active alkaloids. These dosages were later halved. Sixteen cases also had Veriloid. Of the 39 cases 6 had no consistent fall in the diastolic pressure, 7 had a slight fall, 12 an appreciable fall and 4 fell to below 100 mm. diastolic. Of the 10 patients with papilloedema, few results were in a good category. Locket's dosage was rather high and he refers to the occurrence of mental depression in 5 patients, and one of these attempted suicide. Side effects led 4 patients to discontinue treatment. Livesay *et al.* (1954) used 2 mg. four times daily of the alseroxylon fraction which was later increased in some cases. They consider that 8 to 12 mg daily is usually adequate. On these doses they observed a reduction in heart size in 1 of 25 patients, electrocardiographic improvement in 0 out of 30, improvement [illegible] ovement in [illegible], subjective [illegible] out of 10 patients with angina and 9 out of 15 with headache. It is quite clear, however, that in these severe cases the degree of objective improvement on alseroxylon alone is inadequate. Lewis et al. (1956) recorded improvements in 12 out of 15 anginal patients on Rauwolfia therapy.

Livesay et al. (1954) recorded blood pressure reductions in about half of their 43 patients; they separated the unresponsive from the responsive patients. Of group 1, with control diastolic pressures below 120 mm. Hg, 10 responsive patients had blood pressure falls from 203/111 to 163/90. The blood pressure change in the 11 unresponsive patients was from 204/109 to 200/106. Of groups 2 and 3, comprising patients with control diastolic pressures above 120 mm. Hg, the mean change in the blood pressure of 10 responsive patients was from 203/127 to 168/97 mm. Hg and the mean blood pressure change of the 12 unresponsive patients was from 225/135 to 236/129.

There were only 5 patients in group 3 with control diastolic pressures above 140 mm. Hg and only one of these responded to administration of the alseroxylon fraction.

Singh (1955) treated two cases with malignant hypertension and one with chronic nephritis and found comparatively small falls of blood pressure. He found that the side effects were liable to be increased above a dosage level of 0.75 mg. daily of reserpine. Hensler (1953) obtained a useful blood pressure fall in only one out of three cases of malignant hypertension. Hayden (1955) found reserpine effective in only 5 per cent of severe, progressive hypertensive patients.

Doyle, McQueen and Smirk (1955) used reserpine in 40 patients as the sole medication and in 10 of these the blood pressure control was good with normal or near-normal levels. The doses, however, were large and ranged from 0.25 mg. thrice daily to 1.5 mg. thrice daily and were much higher than we would wish to recommend now, because of the risk of mental depression; but the effects on the blood pressure level were definite (Fig. XVII 5). It will be seen that the diurnal fluctuations of the blood pressure took place at a lower level. In severe cases we found that reserpine often produced substantial falls, but only with high doses, up to 9 mg. daily, unsuitable for continued administration. We conclude that in severe cases the principal use for reserpine and other Rauwolfia alkaloids is in combination with ganglion blocking agents (see Chapter XX). When so used, the continued administration of small doses, such as 0.25 to 0.5 mg. of reserpine daily has a definite effect, namely, the requisite dose of the methonium compound is reduced appreciably in all or almost all cases without diminution, and often with improvement, in the hypotensive action.

Large parenteral doses of reserpine (2.5 mg. intramuscularly) have been recommended for the treatment of hypertensive emergencies by Griffin et al. (1956). Dimond and Gonlubol (1955) also used parenteral administration of doses up to 7 mg. but of an average magnitude of 4 mg. Good blood pressure falls were noted in most patients, but some failed to respond. When the patient is in hospital and can be supervised my preference is for the ganglion blocking drugs which act more rapidly.

## REFERENCES

1 ACHOR, R. W. P., HANSON, N. O., and GIFFORD, R. W. Jr. Hypertension treated with Rauwolfia serpentina (whole root) and with reserpine: Controlled study disclosing occasional severe depression. J. Amer. med. Ass., 159: 841, 1955.
1a ARNOLD, O. H., and BOCK, K. D. Neuere Ergebnisse über die medikamentöse Behandlung der arteriellen Hypertonie. Dtsch. med. Wschr., 78: 879, 1953.
2 BARSA, J. A., and KLINE, N. S. Treatment of two hundred disturbed psychotics with reserpine. J. Amer. med. Ass., 158: 110, 1955.
2a BARSA, J. A., and KLINE, N. S. Use of reserpine in disturbed psychotic patients. Amer. J. Psychiat., 112: 684, 1956.
3 BEIN, H. J. Zur Pharmakologie des Reserpin, eines neuen Alkaloids aus Rauwolfia serpentina Benth. Experientia (Basel), 9: 107, 1953.
4 BEIN, H. J. Significance of selected central mechanisms for the analysis of the action of reserpine. Ann. N. Y. Acad. Sci., 61: 4, 1955.
5 BEIN, H. J., GROSS, F., TRIPOD, J., and MEIER, R. Experimentelle Untersuchungen über "Serpasil" (Reserpin), ein neues, sehr wirksames Rauwolfiaalkaloid mit neuartiger zentraler Wirkung. Schweiz. med. Wschr., 83: 1007, 1953.
5a BHARGAVA, K. P., and BORISON, H. L. Comparative effects of some Rauwolfia alkaloids on central vasoregulatory mechanisms. Fed. Proc. 15: 401, 1956.
5b BHATTACHARYA, B. K. and LEWIS, G. P. Comparison of the effect of reserpine and 48/80 on the histamine and 5-hydroxytryptamine in mast cells of rats. J. Physiol. (Lond.), 133: 10p, 1956.
6 BIXBY, E. W., Jr. Rauwolfia and paroxysmal tachycardia. J. Amer. med. Ass., 157: 946, 1955.
7 BLEULER, M., and STOLL, W. A. Clinical use of reserpine in psychiatry: Comparison with chlorpromazine. Ann. N. Y. Acad. Sci., 61: 167, 1955.
8 BODENDORF and EDER, Natura, 40: 342, 1953.
8a BOGDANSKI, D. F., and UDENFRIEND, S. Serotonin and monoamine oxidase in brain. J. Pharmacol., 116: 7, 1956.
9 BOWER, H. M. A clinical evaluation of reserpine in the treatment of chronic mental patients. Med. J. Aust., 2: 82, 1955.
9a BRODIE, B. B., PLETSCHER, A., and SHORE, P. A. Possible role of serotonin in brain function and in reserpine action. J. Pharmacol., 116: 9, 1956.
10 BULBRING, E. Observations on the isolated phrenic nerve diaphragm preparation of the rat. Brit. J. Pharmacol., 1: 38, 1946.
10a BURRELL, R. H. Depression associated with reserpine therapy. N. Z. med. J., 55: 228, 1956.
11 CAHN, C. H. Complication during reserpine therapy — Case reports. Amer. J. Psychiat., 112: 64, 1955.
12 CERLETTI, A., KONZETT, H., and TARSCHLER, M. Canescin, ein mit Reserpin wirkungsgleiches Alkaloid aus Rauwolfia canescens. Experientia (Basel), 11: 99, 1955.
13 CHATTERJEE, A., and BOSE, S. Serpine — A new isomeride of yohimbine isolated from Rauwolfia serpentina benth. Experientia (Basel), 10: 246, 1954.
13a CHESSIN, M., DUBNICK, B., KRAMER, E. R., and SCOTT, C. C. Modifications of pharmacology of reserpine and serotonin by iproniazid. Fed. Proc., 15: 409, 1956.
14 CHOPRA, R. N., BOSE, B. C., GUPTA, J. C., and CHOPRA, I. C. Alkaloids of

Rauwolfia serpentina: A comparative study of their pharmacological action and their role in experimental hypertension Indian J. med. Res, *30:* 319, 1942.

15 CHOPRA, R. N., and CHAKRAVARTI, M. A preliminary note on the pharmacological action of the alkaloids of Rauwolfia serpentina Indian J. med. Res., *29:* 763, 1941.

16 CHOPRA, R. N., GUPTA, J. C., BOSE, B C, and CHOPRA, I. C. Hypnotic effect of Rauwolfia serpentina: The principle underlying this action, its probable nature. Indian J. med. Res, *31:* 71, 1943.

16a COLE, J., and GLEES, P. Ritalin as an antagonist to reserpine in monkeys Lancet, *1:* 338, 1956.

17 CORCORAN, A. C., DUSTAN, H. P., TAYLOR, R. D., and PAGE, I. H Management of hypertensive disease. Amer. J. Med., *17:* 383, 1954.

17a CRONHEIM, G., and GOURZIS, J T. Cardiovascular effects of serotonin in dogs premedicated with reserpine. Fed. Proc., *15:* 414, 1956.

18 CRONHEIM, G, ORCUTT, J. A., and TOEKES, I. M. Pharmacological properties of canescine (recanescine) — A new alkaloid isolated from Rauwolfia canescens Linn. Proc. Soc. exp Biol. (N.Y.), *89:* 21, 1955.

18a CUMMINS, J. F., and BALFOUR, D. C., Jr. Effect of Rauwolfia alkaloids on the excretion of uropepsin in the human. J. Amer med. Ass., *161:* 864, 1956.

19 DAS, N. N., DASGUPTA, S. R., MUKHERJEE, K. L., and WERNER, G. Haemodynamic effects of rauwolscine. Indian J. med Res, *43:* 101, 1955.

20 DASGUPTA, S. R., RAY, G. K, and WERNER, G. Central actions of Rauwolfia serpentina. Indian J. med Sci., *7:* 597, 1953.

21 DAVIES, D L, and SHEPHERD, M. Reserpine in the treatment of anxious and depressed patients. Lancet, *2:* 117, 1955

22 DE JONGH, D. K., and VAN PROOSDIJ-HARTZEMA, E. G Investigation into experimental hypertension. IV The acute effects of Rauwolfia alkaloids on the blood pressure of rats with experimental renal hypertension. Acta physiol pharmacol neerl, *4.* 175, 1955.

23 DELAY, J., DENIKER, P., TARDIEU, Y, and LEMPERIERE, T. Premiers essais de la réserpine — Comparaison avec les effets de la chlorpromazine Press méd, *63:* 663, 1955

24 DENNISON A. D WHITE P. T. MOORE R B., and PIERCE, W. J Effect of reserpine upon the human electroencephalogram Neurology, *5* 56, 1955.

24a DICE, N, BAGCHI, B K, and WAGGONER, R W. Investigation of effects of intravenous reserpine in disturbed psychotic and brain-damaged patients J Nerv ment Dis, *122* 472, 1955

24b DIMOND, E G, and GONLUBOL, F Parenteral reserpine in the management of hypertension Circulation (N Y), *12·* 694, 1955

25 DORFMAN, L., HUEBNER, C F, MACPHILLAMY, H B, SCHLITTER, E, and ST ANDRE, A. F. On the constitution of reserpine from Rauwolfia serpentina Benth Experientia (Basel), *9* 368, 1953

26 DOYLE, A. E, MCQUEEN, E G, and SMIRK, F H. The combination of reserpine (serpasil) and pentamethylene 1 5-bis-n-(n-methyl-pyrrolidinium) bitartrate (Ansolysen) for the control of high blood pressure. Proc. Univ. Otago med. Sch, *32·* 4, 1954

27 DOYLE, A. E., MCQUEEN [illegible] sion with reserpine, dinium, and with re[illegible] Circulation (N.Y), *11:* 170, 1955.

28 DOYLE, A. E., and SMIRK, F. H. Hypotensive action of reserpine. Lancet, 1: 1096, 1954

29 DOYLE, A. E., and SMIRK, F. H. Drug therapy in hypertension — A critical review. Practitioner, 174: 135, 1955.

29a EGDAHL, R. H., RICHARDS, J. B., and HUME, D. M. Effect of reserpine on adrenocortical function in unanesthetized dogs. Science, 123: 418, 1956.

29b ERSPAMER, V. Observations on the 5-hydroxytryptamine (Enteramine) release caused by reserpine in the rat. Experientia (Basel), 12: 63, 1956a.

29c ERSPAMER, V. Some observations on the fate of exogenous 5-hydroxytryptamine (enteramine) in the rat. J. Physiol (Lond.), 113: 1, 1956b.

29d FEINBLATT, T. M., FEINBLATT, H. M., and FERGUSON, E. A. Jr. Rauwolfia-ephedrine as a hypotensive-tranquilizer. J. Amer. med. Ass., 161: 424, 1956

30 FOOTE, E. S. Reserpine in treatment of chronic psychotics — Preliminary observations. Brit. med. J., 1: 1192, 1955.

31 FREIS, E. D. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. New Engl. J. Med., 251: 1006, 1954.

32 FREIS, E. D., and ARI, R. Clinical and experimental effects of reserpine in patients with essential hypertension. Ann. N. Y. Acad. Sci., 59: 45, 1954.

33 GALLAGHER, D. J. A. A medium for perfusion of innervated blood vessels. Brit. J. Pharmacol., 9: 129, 1954.

34 GAUNT, R., RENZI, A. A., ANTONCHAK, N., MILLER, G. J., and GILMAN, M. Endocrine aspects of the pharmacology of reserpine. Ann. N. Y. Acad. Sci., 59: 22, 1954

35 GLYNN, J. D. Rauwolfia serpentina (Serpasil) in psychiatry. J. Neurol. Neurosurg. Psychiat., 18: 225, 1955.

35a GREEN, R. S., and DAVOLOS, D. A long-term study of the effect of crude Rauwolfia serpentina and of its alseroxylon fraction in patients with hypertension. Amer. J. Med., 20: 760, 1956.

35b GRIFFIN, R. W., STOVER, J. W., and FORD, R. Treatment of hypertensive emergencies. Parenteral use of reserpine. New Engl. J. Med., 254: 593, 1956.

36 HAFKENSCHIEL, J. H., and SELLERS, A. M. Intravenous reserpine in patients with essential hypertension. Ann. N. Y. Acad. Sci., 59: 54, 1954

37 HAFKENSCHIEL, J. H., SELLERS, A. M., KING, G. A., and THORNER, M. W. Preliminary observations on the effects of parenteral reserpine on cerebral blood flow, oxygen and glucose metabolism, and electroencephalograms of patients with essential hypertension. Ann. N. Y. Acad. Sci., 61: 78, 1955

37a HAVERBACK, B. J., SHORE, P. A., TOMICH, E. G., and BRODIE, B. B. Cumulative effect of small doses of reserpine on serotonin in man. Fed. Proc., 15: 434, 1956

38 HAYDEN, J. G. The reserpine anti-hypertensive drugs. Med. J. Aust., 2: 223, 1955

39 HENSLER, L. Hypertonietherap [illegible] der Rauwol-

39a [illegible] response to [illegible] for the treatment [illegible] hypertension. Amer. J. med. Sci., 231: 542, 1956.

39b HESS, S. M., SHORE, P. A., and BRODIE, B. B. Persistence of reserpine

action after its disappearance from brain. Fed. Proc., 15: 437, 1956.
39c HODGE, J. V., and MCQUEEN, E. G. Unpublished observations, 1956.
40 HOLLISTER, L. E., KRIEGER, G. E., KRINGEL, A., and ROBERTS, R. H. Treatment of chronic schizophrenic reactions with reserpine. Ann. N. Y. Acad. Sci., 61: 92, 1955.
41 HOOBLER, S. W. Treatment of hypertension. Amer. J. Med., 17: 259, 1954.
41a HORWITZ, B. S., and WANG, S. C. Reserpine effect in medullary vasomotor [illegible] 430, 1956.
42 [illegible] RD, R., and MOYER, J. H. [illegible] hypertension. Amer. J. med. Sci., 228: 21, 1954.
43 HUGHES, W. M., MOYER, J. H., and DAESCHNER, W. C., Jr. Parenteral reserpine in treatment of hypertensive emergencies. Arch. intern. Med., 95: 563, 1955.
44 JERI, R. Effects of reserpine in psychiatric patients. J. Amer. med. Ass., 157: 530, 1955.
44a KAYSER, F. "Vergiftung" mit Reserpin bei einem Kleinkind. Arch. Toxikologie, 16: 97, 1956.
45 KERT, M. J., CARLETON, H. G., NORDYKE, R. A., ROTH, S. I., SMITH, A., and WESTERGART, J. P. Clinical experiences with reserpine (Serpasil) in hypertension Angiology, 6. 138, 1955.
46 KLINE, N. S Use of Rauwolfia serpentina Benth in neuropsychiatric conditions Ann N. Y. Acad. Sci., 59: 107, 1954.
47 KLOHS, M. W., KELLER, F., WILLIAMS, R., and KUSSEROW, G. W. J. Amer. chem Soc., in press. Cited by Cronheim, G., Orcutt, J A., and Toekes, I. M. Proc. Soc. exp. Biol. (N.Y.). 89: 21, 1955.
48 KOEPFLI, J. B. Chemical investigation of Rauwolfia Caffra (I) Rauwolfine. J. Amer chem Soc, 54. 2412, 1931
48a KROGSGAARD, A. R. The effect of intravenously injected reserpine on blood pressure, renal function and sodium excretion Acta med. scand., 154· 41, 1956.
48b KUNTZMAN, R, UDENFRIEND, S., TOMICH, E G, BRODIE, B, and SHORE, P. A Biochemical effect of reserpine on serotonin binding sites. Fed Proc., 15. 450, 1956.
48c KUPPERMAN, H. S, BLATT, M H G., VOSBURGH, L. F, CANIS, J., and WETCHLER, B. Effect of reserpine, with or without hormonal therapy, upon the female climacteric J Amer Geriat Soc., 4. 160, 1956.
49 LAWRENCE, 1912 Cited by Sollmann, T H A Manual of Pharmacology, W. B. Saunders Company, Philadelphia, p 326, 1942.
49a LEMIEUX, G., DAVIGNON, A, and GENEST, J. Depressive states during Rauwolfia therapy for arterial hypertension A report of 30 cases. Canad. med. Ass. J., 74: 522, 1956.
49b LEWIS, B. I, LUBIN, R. I, JANUARY, L E, and WILD, J B Central nervous system and cardiovascular effects of Rauwolfia serpentina. J. Amer med. Ass, 160· 622, 1956.
50 LIM, R K S., MOFFITT, R L., and GLASS, H. G. Observations on the mechanism of central hypotension. J. Pharmacol., 113· 33, 1955
51 LIVESAY, W. R., and MILLER, S. I A comparison of results in the treatment of hypertension with Rauwolfia serpentina alone and in combination with hexamethonium or hydrallazine. J. Pharmacol, 110: 33, 1954
52 LIVESAY, W. R., MOYER, J. H., and MILLER, S. I. Treatment of hypertension with Rauwolfia serpentina alone and combined with other drugs — Results in eighty-four cases. J. Amer med. Ass., 155: 1027, 1954.

53 LOCKET, S. Oral preparations of Rauwolfia serpentina in treatment of essential hypertension. Brit. med. J., 1: 809, 1955.
54 MACARTHUR, J. G., and ISAACS, B. Mental effects of reserpine. Lancet, 2: 347, 1955
54a MCGREGOR, M., and SEGEL, N. The Rauwolfia alkaloids in the treatment of hypertension. Brit. Heart J., 17: 391, 1955
55 MCQUEEN, E. G. Unpublished observations.
56 MCQUEEN, E. G. Mode of action of reserpine. Proc. Univ. Otago med. Sch., 32: 26, 1954.
57 MCQUEEN, E. G., and BLACKMAN, J. G. Direct effects of reserpine, rescinnamine and recanescine on blood vessels. Proc. Univ. Otago med. Sch., 33. 5, 1955a.
58 MCQUEEN, E. G., and BLACKMAN, J. G. Direct effects of reserpine, rescinnamine and canescine on blood vessels. Aust. Ann. Med., 4: 250,

59 [illegible]

60 [illegible]

61 [illegible]
61a MARLEY, E., and PARE, C. M. B [illegible] J., 2: 287, 1956.
61b MAXWELL, R. A., PLUMMER, A. J., ROSS, S. D., and OSBORNE, M. W. Effects of reserpine on urinary bladder tension Proc. exp. Biol. Med. (N.Y.), 92 227, 1956
62 MENDOZA-DAZA, R. Thèse Université de Paris, 1941 Cited by Mezey, K., and Uribe, B., Arch. int Pharmacodyn., 98: 273, 1954.
63 MERCIER, F., and DELPHAUT, J. Sur l'action de l'adrénaline et de l'yohimbine administrées par voie sous occipitale et lombaire. C. R. Soc. Biol. (Paris), 123 24, 19[illegible]
64 MEYER-LEDOIX, H. Die [illegible] loid der Rauwolfia [illegible]
65 MEZEY, K., and URIBE, B. [illegible] plant Arch int Physiol., 98: 273, 1954
66 MONROE, R. R., HEATH, R. G., MICKLE, W. A., and MILLER, W. A comparison of cortical and subcortical brain waves in normal, barbiturate, reserpine and chlorpromazine sleep Ann N. Y. Acad. Sci., 61: 56, 1955
67 MOOKERJEE, A. J. Indian chem Soc., 18. 33, 1941.
68 MOORE, J. N. P., and MARTIN, E. A. Toxic effects of reserpine. Lancet, 1: 1126, 1955.
69 MOORE, R. B., PIERCE, W. J., and DENNISON, A. D. The story of reserpine. J. Indiana med Ass., 47 853, 1954.
69a MORGAN, D. R. The use of reserpine, chlorpromazine and allied drugs in medicine and psychiatry Med J. Aust., 1 1029, 1956.
70 MOYER, J. H. Cardiovascular and renal hemodynamic response to reserpine (Serpasil), and clinical results of using this agent for the treatment of hypertension Ann N Y Acad. Sci., 59. 82, 1954.
71 MUKHERJEE, J. N. Effect of rauwolscine on the action of adrenaline on blood pressure. Nature (Lond.), 172: 867, 1953.
71a MULLER, J. C., PRYOR, W. W., GIBBONS, J. E., and ORGAIN, E. S. Depression and anxiety occurring during Rauwolfia therapy. J. Amer. med Ass., 159 836, 1955
72 MÜLLER, J. M., SCHLITTLER, E., and BEIN, H. J. Reserpin, der sedative

Wirkstoff aus Rauwolfia serpentina Benth. Experientia (Basel), 8: 338, 1952.

73 Noce, R. H., Williams, D. B., and Rapaport, W. Reserpine (Serpasil) in the management of the mentally ill. J. Amer. med. Ass., *158*: 11, 1955.

73a Paasonen, M. K., and Vogt, M. The effect of drugs on the amounts of substance P and 5-hydroxytryptamine in mammalian brain. J. Physiol. (Lond.), **131**: *617*, *1956*.

73b Packman, E. W., Abbott, D. D., and Harrisson, J. W. C. A preliminary study of the pharmacology of 11-desmethoxyreserpine (Raunormine) an alkaloid from Rauwolfia canescens II. J. Amer. pharm. Ass., 45: 89, 1956

73c Parratt, J. R., and West, G. B. Tissue histamine and 5-hydroxytryptamine. J. Physiol. (Lond.), **132**: *40p*, *1956*.

74 Perera, G. A. Rauwolfia serpentina in hypertensive vascular disease. Proc. Soc exp. Biol. (N.Y.), *86*: *453*, *1954*

74a Platt, R., and Sears, H. T. N Reserpine in severe hypertension. Lancet, 1: 401, 1956.

74b Pletscher, A., Shore, P. A., and Brodie, B. B. Release of brain serotonin by reserpine. J. Pharmacol., *116*: *46*, *1956a*.

74c Pletscher, A., Shore, P. A., and Brodie, B. B. Serotonin as a mediator of reserpine action in brain. J Pharmacol., *116*: *84*, 1956b.

75 Plummer, A. J., Earl, A., Schneider, J. A., Trapold, J., and Barrett, W. Pharmacology of Rauwolfia alkaloids, including reserpine. Ann N. Y. Acad. Sci., *59*: *8*, *1954*.

76 Putz, F., and Spies, R. Fortschritte in der behandlung der arteriellen hypertonie. Wien med. Wschr., **104**. 202, 1954.

77 Ray, P C The hypnotic action of Rauwolfia serpentina (Dhan Marua). Patna J. Med, *6*: *193*, *1931*

78 Raymond-Hamet, M Sur un nouveau paralysant électif des vasoconstricteurs adrénalino-sensibles l'ajmalinine, alcaloïde cristallisé de l'ophioxylum serpentinium Willd Bull Acad Méd (Paris), **115**: *452*, *1936*

79 Raymond-Hamet, M. Sur quelques propriétés physiologiques de la serpentine, alcaloïde cristallisé du Rauwolfia serpentina Bentham C R Soc. Biol (Paris), **134**: *94*, *1940*.

80 Raymond-Hamet, M Effets tenseurs et vasculaires d'un des alcaloïdes colorés du Rauwolfia serpentina Bentham C R acad. Sci. (Paris), **223**: *927*, *1946*

81 Rea, E. L., and Fazekas, J F Effects of parenterally administered reserpine. Arch intern Med, **95**: *538*, *1955*

82 Richman, A., and Tyhurst, J. S An extrapyramidal syndrome with reserpine Canad. med Ass J, *72*: *457*, *1955*

83 Sainz, A A. The use of reserpine in ambulatory and hospitalized geriatric psychotics Ann N. Y. Acad. Sci, *61* *72*, *1955*.

83a Sarwer-Foner, G. J., and Ogle, W Psychosis and enhanced anxiety produced by reserpine and chlorpromazine Canad. med Ass. J, *74*: *526*, *1956*.

84 Schlittler, E, Saner, H, and Muller, J. M Reserpinin ein neues Alkaloid aus "Rauwolfia serpentina" Benth. Experientia (Basel), **10**: 133, 1954

85 Schlittler, E., Ulshafer, P R, Pandow, M L, Hunt, R M, and Dorfman, L. Rauwolfia alkaloids XVI. Deserpidine, a new alkaloid from Rauwolfia canescens. Experientia (Basel), **11**. *64*, *1955*

86 Schneider, J. A. Further characterization of central effects of reserpine (Serpasil). Amer J. Physiol, **181**: *64*, *1955*.

86a SCHNEIDER, J. A., PLUMMER, A. J., EARL, A. E., BARRETT, W. E., RINEHART, R., and DIBBLE, R. C. Pharmacological studies with deserpidine, a new alkaloid from Rauwolfia canescens. J. Pharmacol, 114: 10, 1955.
86b SCHNEIDER, J. A, and RINEHART, R. K. Pharmacological interactions of serotonin and reserpine in dogs. J. Pharmacol, 116: 51, 1956.
86c SCHROEDER, H. A., and PERRY, H. M., Jr. Psychosis apparently produced by reserpine. J Amer. med. Ass, 159: 839, 1955.
87 SEN, G., and BOSE, K. C. Rauwolfia serpentina, a new Indian drug for insanity and high blood pressure Indian med. World, 2: 194, 1931.
87a SHORE, P A., PLETSCHER, A., TOMICH, E G, KUNTZMAN, R, and BRODIE, B B. Release of blood platelet serotonin by reserpine and lack of effect on bleeding time. J Pharmacol., 117: 232, 1956.
88 SHUMAN, J S. Paralysis agitans developing during reserpine therapy. J Amer med Ass, 158: 73, 1955.
89 SIDDIQUI, S., and SIDDIQUI, R. H. J. Indian chem. Soc, 8: 667, 1931.
90 SIDDIQUI, S S., and SIDDIQUI, R. H. A note on the alkaloids Rauwolfia serpentina, Benth J Indian chem. Soc., 16: 421, 1939.
91 SINGH, I Reserpine in hypertension. Brit. med. J., 1: 813, 1955.
92 SLATER, I. H, RATHBUN, R. C, HENDERSON, F. G, and NEUSS, N. Pharmacological properties of recanescine, a new sedative alkaloid from Rauwolfia canescens Linn. Proc Soc exp. Biol. (N.Y), 88: 293, 1955
93 SMIRK, F H Unpublished observations
94 SMIRK, F. H R waves interrupting T waves Brit. Heart J., 11: 23, 1949.
95 SMIRK, F H, DOYLE, A E, and MCQUEEN, E G Control of blood-pressure by combined action of reserpine and pentapyrrolidinium. Lancet, 2. 159, 1954.
96 SMIRK, F H, and MCQUEEN, E G Comparison of rescinnamine and reserpine as hypotensive agents. Proc Univ Otago med Sch., 33: 10, 1955a
97 SMIRK, F H, and MCQUEEN, E G Comparison of rescinnamine and reserpine as hypotensive agents Lancet, 2: 115, 1955b
98 SMITH, S K. The use of reserpine in private psychiatric practice. Ann. N Y Acad. Sci, 61 206, 1955
99 STAPPENBECK, G. Über die Hypertoniebehandlung mit Rauwolfia serpentina Dtsch med J, 5 31, 1954
100 STEAD, J. S, and WING, J K Parkinsonism during treatment with reserpine. Lancet, 1. 823, 1955
100a STEIN, D H, and HECHT, H. H Observation on the effect of a Rauwolfia alkaloid (reserpine) in ambulatory patients with essential hypert[illegible] (Philad), 7· 974, 1956.
[illegible] die Wirkung von Serpasil auf [illegible] Schweiz med. Wschr, 86: 415, 1956
101 STOLL, A, and HOFMANN, A Sarpagin, ein neues Alkaloid aus Rauwolfia serpentina Benth Helv chim Acta, 36. 1143, 1953.
102 STOLL, A, and HOFFMANN, A Canescine and pseudoyohimbine from the roots of Rauwolfia canescens L J Amer. chem Soc 77· [illegible]
103 TRA[illegible]
104 TRI[illegible] von Rauwolfia serpentina B) auf isolierte Kreislauforgane. Arch. int Pharmacodyn, 97. 251, 1954

105 TUCHMAN, H., SLETTEN, I. W., and CRUMPTON, C. W. A clinical study of the effects of intravenous reserpine (Serpasil) in hypertensive patients. Amer. Heart J., 48: 449, 1954.
106 TWEEDY, P. S. Treatment of hypertension. Lancet, 2: 249, 1955.
107 TYHURST, J. S., and RICHMAN, A. Clinical experience with psychiatric patients on reserpine — Preliminary impressions. Canad. med. Ass. J., 72: 458, 1955.
108 VAKIL, R. J. Clinical trial of Rauwolfia serpentina in essential hypertension. Brit. Heart J., 11: 350, 1949.
109 VAKIL, R. J. Rauwolfia serpentina in the treatment of high blood pressure. Lancet, 2: 726, 1954.
110 VAKIL, R. J. Rauwolfia serpentina treatment of high blood pressure. Acta med. scand., 152: 107, 1955.
111 WALLACE, D. C. Treatment of hypertension — Hypotensive drugs and mental changes. Lancet, 2: 116, 1955.
112 WILKINS, R. W. Rauwolfia in the treatment of essential hypertension. Amer. J. Med., 17: 703, 1954a.
113 WILKINS, R. W. Clinical usage of Rauwolfia alkaloids, including reserpine (Serpasil). Ann. N. Y. Acad. Sci., 59: 36, 1954b.
113a WILKINS, R. W. Serotonin, antiserotonins and hypertension. New Engl. J. Med., 255: 115, 1956.
114 WILKINS, R. W., JUDSON, W. E., STONE, R. W., HOLLANDER, W., HUCKABEE, W. E., and FRIEDMAN, I. H. Reserpine in the treatment of hypertension. New Engl. J. Med., 250: 477, 1954.
115 WINSOR, T. Human pharmacology of reserpine. Ann. N. Y. Acad. Sci., 59: 61, 1954.
115a WOOLLEY, D. W., and SHAW, E. N. Antiserotonins in hypertension and the antimetabolite approach to chemotherapy. Science, 124: 34, 1956.
116 YOUNGKEN, H. W. A pharmacognostical study of Rauwolfia. J. Amer. pharm. Ass., 43: 70, 1954.

CHAPTER XVIII

# PHARMACOLOGY OF GANGLION BLOCKING DRUGS

. . . in quaternary ammonium bases . . . in 1868, long before evidence be . . . also a quaternary ammonium

. . . prising, therefore, that several other quaternary ammonium compounds were found to have properties of great interest, and as knowledge of their effects on physiological processes accumulated, the study of their mode of action became a fruitful source of information concerning the physiology of nervous tissues. It has now been demonstrated that some of these actions are possessed also by certain secondary amines, where the nitrogen is trivalent.

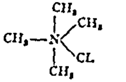
Such properties as penetration of the blood brain barrier and, perhaps, access to ganglia, appear to be much influenced, not only by the chemical structure of the electrically charged head (quaternary grouping), but also by the rest of the molecule. The manner in which the molecule of the drug fits into the physical or chemical system characterizing a particular receptor region may determine the nature of its action there.

. . . that activity will be found sometimes at sites other than the autonomic ganglia

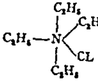
Attention is directed to the formula of acetylcholine, which substance, apparently, is liberated in the region of the end-plates of motor nerves, in autonomic ganglia and at the parasympathetic nerve endings, and even within the central nervous system it seems to play some part in determining nervous activity.

In 1915 Burn and Dale described the difference between the actions of tetramethyl- and tetraethylammonium salts. Tetramethylammonium acts like nicotine, in that it first stimulates the end-plates of the nerves to voluntary muscle and subsequently blocks transmission of

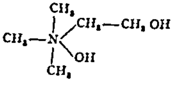
the nerve impulse, but tetraethylammonium has comparatively little action on voluntary muscle. Tetramethylammonium also has a nicotinic action on sympathetic ganglia which are first stimulated and later depressed. Tetraethylammonium depresses ganglia without causing initial stimulation.



Tetra methyl ammonium chloride



Tetra ethyl ammonium chloride



Acetylcholine

Many years of work by Ing on the paralyzing actions of onium compounds led to an attempt by Barlow and Ing (1948) to find the degree of separation of two quaternary ammonium groups within the same molecule which conferred maximum curare-like properties. They found that decamethonium, with ten $CH_2$ groups between the two quaternary ammonium groups, showed a high degree of curare-like activity and caused neuromuscular block with paralysis of the striped muscle. Simultaneously, Paton and Zaimis (1948a) were conducting investigations in the same field. They noted that pentamethonium and hexamethonium, with five and six $CH_2$ groups respectively between the quaternary ammoniums, had their main effect upon the sympathetic ganglia. Their action on ganglia resembled that of tetraethylammonium much more closely than that of tetramethylammonium, for tetraethylammonium, hexamethonium and pentamethonium depress the ganglia without a period of initial stimulation.

When very large doses of penta- or hexamethonium are given, other actions are noted which depend also on interference with acetylcholine transmission in nervous system locations. For example, at neuromuscular junctions very large doses of pentamethonium or hexamethonium may cause curare-like effects in the rabbit which are probably due to their competition with acetylcholine (Paton and Zaimis, 1952), and not to the long-lasting depolarization of the end-plate region, which seems to be the explanation of the curare-like action of decamethonium.

Evidence is accumulating that hexamethonium has central nervous system actions. Recently Dontas and Nickerson (1955) found that hexamethonium reduced the activity of the preganglionic sympathetic

nerves. This last observation suggests that the blood pressure reduction induced by hexamethonium is due, in part, to inhibition of the central nervous system. Other bis-quaternary hypotensive agents described by Cavallito et al. (1955) have been shown to have a central hypotensive a [illegible] that the composition of various quaternary amm[illegible]

and in this way may [illegible] neuromuscular, ganglionic, central nervous, muscarinic (stimulating parasympathetic nerve endings) or atropine-like. Thus, although in 1957 the methonium compounds in use clinically have actions which are largely concerned with the decrease of sympathetic and parasympathetic activity at ganglia, the probability must be borne in mind that important variations in the location and intensity of action may be found among new homologues, some of which will be clinically useful.

Antagonism between hexamethonium and acetylcholine has been demonstrated also at sensory nerve terminals. Coon and Rothman [illegible] that acetylcholine can [illegible] no ganglia occur), and [illegible], even though hexamethonium has no local anaesthetic action. In human subjects Keele et al. (1953) showed that if acetylcholine was applied to the exposed base of a cantharidine blister, pain was induced. This pain was readily antagonized by the previous application of hexamethonium. Douglas (1952) also noted that the carotid body responses to acetylcholine, nicotine and lobeline were blocked by hexamethonium though the [illegible] to evoke responses. [illegible] could conceivably in[illegible] (1) interfering with the liberation of acetylcholine, (2) effects on choline esterase, (3) competition with acetylcholine for receptors, or (4) by causing synaptic unresponsiveness due to lasting depolarization.

Paton and his colleagues have shown that, after hexamethonium, acetylcholine is liberated normally [224], there is no significant effect on choline esterase and no electrical evidence of depolarization [108, 109], or of the initial stimulation which (as in the case of nicotine) precedes unresponsiveness due to depolarization [108, 109]. The blockade of ganglia by competition appears to be the best explanation of paralysis not preceded by stimulation. Apparently the transmission across the ganglionic synapse is effected by acetylcholine and the hexamethonium molecule is insufficiently closely related to acetylcholine to effect a stimulation of the distal terminals of the synapse.

While the actions of hexamethonium appear to be due to interference with acetylcholine reactions, it is worth recollecting that other chemical substances related to acetylcholine may have actions such as

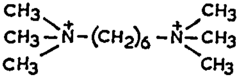
histamine liberation and ganglionic stimulation, and the occurrence of such properties must be sought for in new drugs.

In their 1952 review Paton and Zaimis refer to the fundamental work which preceded and led to the study of methonium compounds and conclude with the following remarks, "The growth of electrical recording methods, of synthetic chemistry, and of clinical trial and investigation have all played their part. But reflection on the fundamental ideas involved and experimental techniques required show that among the developments leading to this therapeutic harvest, the bringing to fruition of the theory of chemical transmission at the neuromuscular and ganglionic synapses must occupy pride of place." To be remembered in connection with this work are the names of Dale, Elliott and Loewi, and more recently of Burn, Feldberg, Brown, Eccles, Ing and of Paton with his colleague Zaimis. Pharmacological and clinical studies on tetraethylammonium by Moe, Acheson and Hoobler were important in directing attention towards the clinical potentialities of ganglion blocking drugs.

## EXPERIMENTAL PHARMACOLOGY OF GANGLION BLOCKING DRUGS

### Hexamethonium

The number of methonium compounds and allied ganglion blocking agents is so considerable that no attempt could be made to describe the properties in detail, even of those which appear to be clinically valuable. Most of the basic work was done first with hexamethonium. The related drugs which are used clinically share most of the properties of hexamethonium and the individual characteristics in which they differ from it will be described in more detail.



Hexamethonium

### Effects on Ganglia

There is no doubt that hexamethonium causes blockade of autonomic ganglia, the most satisfactory evidence being derived from studies of the superior cervical ganglion which lends itself to experimental investigations, since it can be perfused and the pre- and post-ganglionic nerves can be identified readily. Furthermore, the post-ganglionic nerves supply the nictitating membrane, of which the contractions and relaxations are recorded readily. This test object was used by Paton

and Zaimis (1948b, 1951) who found that hexamethonium inhibited the effect of pre-ganglionic stimulation but had no action on post-ganglionic stimulation. Reasons have been given already for believing [illegible] acts by competing with acetylcholine at the [illegible]

[illegible] ganglion.

## Circulatory Effects

[illegible] the falls of blood pressure after administration [illegible]

attained in the whole animal hexamethonium has no significant effect on the muscular action of the isolated cat's heart when added to perfusion fluid (Wien and Mason, 1951). When much larger doses were used, a slight increase in the cardiac activity was noted. The coronary flow of the isolated cat's heart was uninfluenced by hexamethonium also until unphysiological concentrations were employed, when there was a slight increase (Wien and Mason, 1951). In the innervated dog's heart hexamethonium caused no striking effect on the coronary outflow. Changes in cardiac output after hexamethonium are unlikely, therefore, to be due to direct action on the heart muscle but might occur as the result of blockade of nervous impulses to the heart or by alteration in the return of blood to the heart. The effects in lower animals and in man must not be expected to correspond exactly. The sympathetic system is much more important in man than in many lower animals, because in man there is the need to make large adjustments in the state of contraction of blood vessels to combat gravitational changes in intravascular pressure in the upright posture.

*Effect on blood pressure* — In the cat Paton and Zaimis (1951) noted the falls of blood pressure which follow intravenous injections. Usually the falls were greater when the blood pressure was high than when it was low. As the dose of hexamethonium was increased, the blood pressure fell to about 60 to 80 mm. Hg, after which dosage increase caused no further blood pressure fall. Paton and Zaimis (1951) showed further that when the blood pressure is first raised by asphyxia, hexamethonium causes a larger blood pressure fall.

Fastier and his colleagues (1956) studied the falls of blood pressure with hexamethonium and its homologues in unanaesthetized rabbits. They found that the intravenous administration of 5 mg. of hexamethonium per kg. body weight produces an average fall of 30 mm. Hg in the mean blood pressure of the rabbit. At the same time, the blood pressure fall was associated with dilatation of the ear vessels,

indicating that dilatation of blood vessels must be playing some part in the blood pressure fall.

An action of great interest described by Paton and Zaimis (1951) is that the rises of blood pressure from ganglion stimulation by either nicotine or tetramethylammonium were much diminished by hexamethonium.

Paton and Zaimis (1951) found, as one would expect, that in the

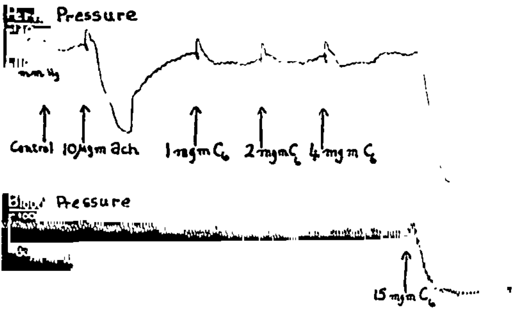



Fig. XVIII 1

Rabbit, hind-limb perfused independently, simultaneous reccords of arterial blood pressure and perfusion pressure Injection of acetyl choline (10 $\mu g$) and of hexamethonium bromide (1, 2 and 4 mg. $C_6$) into perfusate, injection of hexamethonium bromide intravenously (15 mg. $C_6$) (Gallagher, D J A., Brit J Pharmacol, 9 129, 1954).

pithed spinal animal there was no depressor action at all from methonium salts. They concluded that pentamethonium and hexamethonium acted by paralyzing autonomic ganglia and that they were without action on the effector cells. They did not concern themselves with the additional possibility of a central action.

*Effects on blood pressure regulation.* — An action on the carotid sinus reflex is to be expected from the observation of Bartorelli et al. (1954) who state that, after hexamethonium, bilateral clamping of the carotid arteries no longer causes an increase in blood pressure.

The preparation devised by my colleague Gallagher (1954a) makes

it possible to study the effect of hexamethonium on the nervous regulation of vascular tone. The preparation consists of an anaesthetized rabbit with the circulation to a lower limb isolated from the rest of the body and perfused at a constant rate, using a special perfusion medium consisting of Kreb's solution, dextran, and washed human or sheep red cells. This preserves nervous activity in the perfused parts of

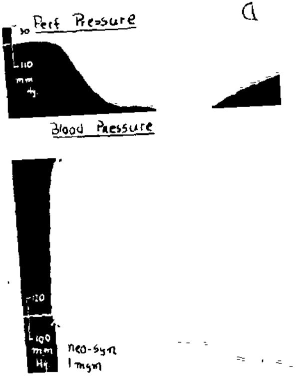



Fig. XVIII 2

Rabbit, hind-limb perfused independently, simultaneous records of arterial blood pressure and perfusion pressure Injection of 1 mg neosynephrine intravenously raised the blood pressure and led to a decrease in the perfusion pressure through the hind-limb

the rabbit When hexamethonium is injected into the perfused hind limb no change in the perfusion pressure results, indicating the absence of any important direct action on blood vessels. When the hexamethonium is injected into the upper half of the rabbit there is a fall in the perfusion pressure, indicating dilatation of the blood vessels of the hind limb (Fig XVIII 1.) When a pressor agent, such as adrenaline, is injected into the upper part of the animal a fall of perfusion pressure occurs in the hind limb, due to the operation of homeostatic reflexes (Fig. XVIII

2). If a drug which acts directly on the blood vessels, such as acetylcholine or amyl nitrite, is introduced into the upper half of the animal there is an increase in sympathetic activity, representing an attempt at nervous homeostasis (Fig. XVIII 3). This leads to vasoconstriction and a rise in the perfusion pressure in the hind limb to which the drug is denied access. The rises of pressure due to the operation of these homeostatic mechanisms are abolished by the previous administration of hexamethonium to the upper half of the rabbit. These results have been amply confirmed and extended by my colleagues Field and Laverty (unpublished) by pump-controlled cross-circulation experiments between pairs of rabbits, but not using Gallagher's artificial blood-dextran medium.

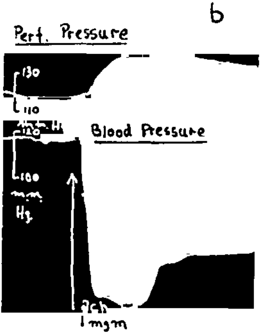



Fig. XVIII 3

R
pres
the
limb

Attention is directed particularly to these experiments for they demonstrate that dilatation of blood vessels plays a part in causing blood pressure falls in the rabbit. If, however, there is also a decrease in the cardiac output, then this factor also must be concerned in the blood pressure fall. They made, also, cross-circulation experiments between rats. An innervated rat hind limb was perfused through the femoral artery by blood from a donor rat and returned from the femoral vein

of the recipient to the donor. Although the blood vessels of the rat hind limb were under nervous control and reacted appropriately to asphyxia and to hexamethonium, there was usually little nervous reaction to the administration of pressor agents such as adrenaline or depressor agents such as acetylcholine into the upper part of the rat. Gallagher had also observed greater reactivity to neurogenic stimuli in the rabbit hind limb.

In the dog it seems likely from the work of Murphy et al. (1953) and Crumpton et al. (1953) that hexamethonium induces a decrease in the cardiac output. Probably the effect is due to decrease in the return of blood to the heart as the result of dilatation in veins and venules. There are, however, other actions for, as Paton and Zaimis showed, hexamethonium prevents bradycardia from vagal stimulation. Waud et al. (1955) have shown that the blood pressure fall is not dependent on diminished cardiac output as it occurs in dogs after replacing the heart and lungs by a pump and oxygenator. The relationship of decrease in cardiac output to decrease in peripheral resistance will be discussed in the section on clinical pharmacology.

In animals and in man the pressor actions of adrenaline and noradrenaline are enhanced when hexamethonium has been given beforehand. The reactions of the innervated perfused rabbit hindlimb preparation devised by Gallagher (1954 a, b), and referred to earlier, throw some light on this phenomenon. When noradrenaline is injected into the upper part of the animal the rise of blood pressure excites a homeostatic response leading to decrease of sympathetic activity. This is shown by a decrease in the peripheral resistance in the rabbit limb with a fall in the perfusion pressure. After a large dose of hexamethonium has been administered to the head end of the animal there is a great decrease of the peripheral resistance in the blood vessels of the perfused hindlimb, and injections of noradrenaline which raise the blood pressure in the head end of the animal have no effect on the perfusion pressure in the hind limb. In the head end of the animal the expected increase in the response to noradrenaline after hexamethonium occurred as usual

It seems clear that inhibition of homeostatic reflexes by hexamethonium is at least part of the explanation of its effect of potentiating the action of adrenaline.

*Effects on the renal circulation.* — Moyer and Mills (1953) have found that hexamethonium decreases the glomerular filtration rate, but even while the blood pressure remains at a low level, there is usually a return to the original levels. The urine flow which decreases initially returns later towards normal.

*Effects on the cerebral circulation.* — Poole (1954) studied the pial circulation of cats through skull windows and showed that dilatation of arteries was often associated with the fall of blood pressure induced

2). If a drug which acts directly on the blood vessels, such as acetylcholine or amyl nitrite, is introduced into the upper half of the animal there is an increase in sympathetic activity, representing an attempt at nervous homeostasis (Fig. XVIII 3). This leads to vasoconstriction and a rise in the perfusion pressure in the hind limb to which the drug is denied access. The rises of pressure due to the operation of these homeostatic mechanisms are abolished by the previous administration of hexamethonium to the upper half of the rabbit. These results have been amply confirmed and extended by my colleagues Field and Laverty (unpublished) by pump-controlled cross-circulation experiments between pairs of rabbits, but not using Gallagher's artificial blood-dextran medium.

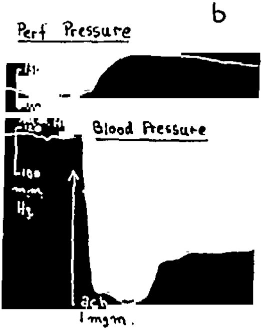



Fig XVIII 3

limb

Attention is directed particularly to these experiments for they demonstrate that dilatation of blood vessels plays a part in causing blood pressure falls in the rabbit. If, however, there is also a decrease in the cardiac output, then this factor also must be concerned in the blood pressure fall. They made, also, cross-circulation experiments between rats. An innervated rat hind limb was perfused through the femoral artery by blood from a donor rat and returned from the femoral vein

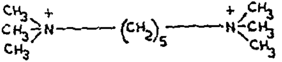
and Wien and his co-workers[87, 153, 154, 155, 156, 159] in particular have surveyed several homologous series of compounds and their results ... compounds depends upon their position in

... They ...

are tolerated when adr ... 

Most of the detailed ... been done on hexamethonium; to a lesser ... er compounds, though now more important clinically, have not been so extensively studied in laboratory animals, but some of them have been studied closely in man.

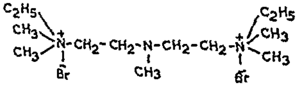
### Pentamethonium



Pentamethonium

The differences between hexamethonium and pentamethonium are so slight in experimental animals that in almost all experiments its action closely approximates to, or is indistinguishable from, the action of hexamethonium.

### N,N,N', N'-3-Pentamethyl-N, N'-Diethyl-3-Aza-Pentane-1,5-Diammonium-Dibromide (Pendiomide, Ciba, 9295)



CIBA 9295

The action of Pendiomide resembles closely that of hexamethonium, but it is somewhat less active and drug toleration develops to a greater degree. As a hypotensive agent it has been superseded

Following Pendiomide administration, substantial blood pressure falls occur in most laboratory animals. Perfused hearts are unaffected[14] but in the whole animal effects on the heart rate depend on whether the vagus or sympathetic

by hexamethonium. The degree of dilatation of vessels is not uniform but is of appreciable degree in some vessels despite the fall of blood pressure.

## Other Effects of Hexamethonium

The non-circulatory effects of hexamethonium in animals will be described briefly, further details being available in the review by Paton and Zaimis (1952).

In the alimentary tract actions vary in a way which might be explained by predominance either of sympathetic or of parasympathetic activity in different species. The spontaneous peristaltic activity of the guinea-pig ileum is inhibited, but acetylcholine or histamine still induces contractions (Feldberg, 1951). Peristaltic activity is also decreased in the rabbit and usually in man, but in the cat there is an increase in the spontaneous activity of the intestines and the stomach *in situ* (Paton and Zaimis, 1951; Wien and Mason, 1951). Dreyer (1954) reported stimulation even of the isolated intestine of the cat; wl [illegible]

paralysed, but test meals and histamine continue to induce secretion (Wien and Mason, 1951). Salivary secretion in response to stimulation of the chorda tympani nerve is paralysed, but the response to carbachol persists. Such effects as dilatation of the mouse pupil under standard illumination, and ptosis of the eyelids in the mouse, are of value in preliminary studies of the action of new ganglion blocking agents. An interesting metabolic effect is the potentiation of insulin hypoglycaemia by hexamethonium in dogs (Schachter, 1951) and in rabbits (Laurence and Stacey, 1951).

Drug toleration to hexamethonium and its analogues is exhibited in animal preparations. Mohanty (1955) considered that toleration could be demonstrated in isolated preparations from animals previously treated with hexamethonium. Tolerance could not be induced by the application of hexamethonium to isolated ganglion preparations from untreated animals.

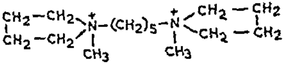
Following injection, hexamethonium is distributed in a volume which corresponds to about 10 to 30 per cent of the total body volume (Morrison and Paton, unpublished), and is presumably confined mainly to the extracellular spaces. It is excreted unchanged in the urine and a large proportion of the administered dose can be recovered (Zaimis, 1950).

## Hexamethonium Analogues

Pharmacological studies have been made on many compounds which are related chemically to hexamethonium. Paton and Zaimis (1949)

*drop test* (for curare-like activity), showed slightly more activity for M. & B. 1863. It also had a stronger effect on gastric secretion.

## Pentolinium (Pentapyrrolidinium, M. & B. 2050A, Ansolysen)



Pentapyrrolidinium
(Pentolinium)

The pentolinium series of compounds was synthesized by Libman, Pain and Slack (1952). Mason and Wien (1955) showed that pentolinium blocked conduction through the superior cervical ganglion and caused relaxation of the nictitating membrane without interfering with the liberation of acetylcholine, which takes place normally on pre-ganglionic stimulation. They showed that, after pentolinium, the nictitating membrane contracted to post-ganglionic stimulation.

The stimulating effect of nicotine on the guinea-pig ileum was abolished by concentrations of pentolinium which did not modify the effects of acetylcholine or histamine. The fall of blood pressure which follows stimulation of the vagus nerve in the anaesthetized rat was abolished, but the effect of acetylcholine on the blood pressure was unmodified. Such experiments demonstrate that the effect of pentolinium on ganglia is similar to that of hexamethonium.

Fastier, Blackman, Wong and Patel (1956) compared the effects of hexamethonium and pentolinium on the blood pressure of the unanaesthetized rabbit. The potency of pentolinium was approximately five times that of hexamethonium. Other effects induced by pentolinium are: inhibition of the salivary flow in response to the excitation of the chorda-lingual nerve, inhibition of the peristaltic reflex of the ileum, mydriasis in the cat and mouse, and inhibition of the bladder contractions induced by stimulation of the vesical branches of one pelvic nerve (Wien, 1954a).

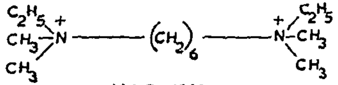
Mason and Wien (1955) found that a large proportion of an intravenously administered dose of pentolinium in rabbits was excreted in the urine within two days, whereas only about 20 per cent of a 50 mg./kg dose administered orally was excreted in the urine. They found the duration of action of pentolinium to be slightly longer than that of hexamethonium.

tone predominates. After administration of Pendiomide the pressor action of adrenaline and noradrenaline is increased [11], presumably due to inhibition of the regulatory mechanism. If a considerable rise of blood pressure is produced by the administration of adrenaline, noradrenaline, tyramine, ephedrine, or renin, then the subsequent administration of Pendiomide does not reduce the blood pressure [11], presumably because the pressor agents, by their action on the regulatory centres, have caused a decrease in the amount of neurogenically maintained tone. The blood pressure rise which normally follows bilateral occlusion of the carotid arteries (a carotid sinus reflex) is inhibited by the administration of Pendiomide [11, 12]. It is of interest that Pendiomide prevents the discharge of adrenaline from the suprarenal gland after splanchnic stimulation in the cat [11].

Using the Rein's thermostrumuhr, increases in the femoral, splanchnic and coronary blood flows were observed in the cat after Pendiomide [12]. If very large doses of Pendiomide were administered, the coronary blood flow diminished. The pulmonary artery flow was usually diminished. Intra-arterial injections did not lead to any increase in the blood flow [12] and perfusion of the rabbit's leg with concentrations of Pendiomide as high as $10^{-4}$ did not increase the blood flow.

The usual parasympathetic effects of ganglion blocking drugs occur with Pendiomide.

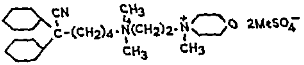
### Hexamethylene Bis-Ethyldimethylammonium (M. & B. 1863, Gaplegin)



M.& B. 1863

Wien and Mason (1951) found that, in their action on autonomic ganglia, most higher homologues of hexamethonium were considerably less potent than hexamethonium. Bis-ethyldimethylammonium was a surprising exception. Qualitatively its actions resemble those of hexamethonium but its potency is 1.5 to 2 times as great. Thus Wien and Mason (1951) found it 1½ times as active as hexamethonium on the superior cervical ganglion of the cat, twice as active on the guinea-pig ileum and twice as active on the cat's blood pressure. The fall of blood pressure which normally takes place on vagus nerve stimulation was inhibited by M. & B. 1863, the drug being twice as active in this respect as hexamethonium. The rabbit phrenic nerve diaphragm preparation showed that there was rather more neuromuscular blockade with M. & B. 1863 than with hexamethonium. Likewise, the rabbit head-

N'-(5-cyano-5-5-diphenylpentyl)-N' : N' : N³-trimethylethylene -1-ammonium-2-morpholinium bis methylsulphate, (139 C 55, Presidal)

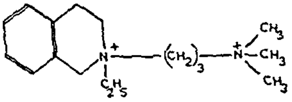


139c55

356 C 54 and 139 C 55 are members of a large series of powerful ganglion blocking drugs of which, at present, 139 C 55 appears to be the most interesting.

The pharmacological effects of 139 C 55 are qualitatively similar to those of hexamethonium, pentolinium and chlorisondamine. Adamson et al. (1956) find that, in cats and dogs, the action is more prolonged and the effective dose smaller than those of hexamethonium or pento- [illegible] ...tating membrane of [illegible] ganglion but leaves [illegible] causes mydriasis in mice and inhibits gastric secretion in fasted Shay rats. This series of compounds merits further study.

IN 292



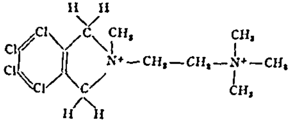
I.N 292

Great interest attaches to the report from Cavallito et al. (1955) of a group of quaternary ammonium derivatives which they find, by cross circulation experiments, decrease the blood pressure mainly by central nervous inhibition. A new compound IN 391 has been developed by Irwin Neisler and Company which has a similar mode of action but is more potent

**Mecamylamine (Inversine)**

A preliminary communication from Dr. Karl H. Beyer Jnr. on the results obtained in the research laboratories of Sharp and Dohme Division of Merck & Co. Inc. describes in some detail the chemical and pharmacological characteristics of mecamylamine, a secondary amine with ganglion blocking properties similar to those possessed by

**4, 5, 6, 7-Tetrachloro-2-(Dimethylaminoethyl)-Isoindoline Dimethochloride (chlorisondamine chloride, Ecolid, Su 3088)**



SU 3088

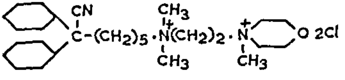
Observations on the pharmacology of chlorisondamine by Plummer, Trapold, Schneider, Maxwell and Earl (1955) revealed properties which are qualitatively similar to those of other ganglion blocking agents. There is inhibition of the superior cervical ganglion in the cat, with preservation of activity of the nictitating membrane to post-ganglionic stimulation. The hypotensive action in dogs of chlorisondamine was larger and more prolonged than that of hexamethonium. In dogs the fall of blood pressure was associated with a decrease in the blood flow through the aorta, mesenteric and renal vessels. There was a temporary

musculature of the cat heart nor on the coronary flow in the cat or dog.

Grimson et al. (1955) noted potentiation of the action of adrenaline, inhibition of the pressor reflex from the carotid sinus and inhibition of the bradycardia and blood pressure depression which normally follow vagal nerve stimulation. The experiments were made in dogs and show that chlorisondamine resembles hexamethonium in its actions on the circulation. Maxwell et al. (1956) found that the pressor response to annoying stimuli in unanaesthetized dogs with neurogenic hypertension was suppressed by chlorisondamine.

Plummer et al. (1955) found that in dogs drug toleration was not pronounced, at least to the relaxing effect of chlorisondamine on the nictitating membrane.

**N′ : N′ : N²-trimethyl-N′-(6-cyano-6; 6-diphenylhexyl) ethylene-1-ammonium-2-morpholinium dichloride, (356 C 54)**



356c54

and

the whole a[illegible]
tion. When [illegible]
unimpaired, falls in the cardiac output are [illegible] pensatory increases in the peripheral resistance, and falls in the peripheral resistance are associated with increases in the cardiac output. Hence, in general, drug action only induces a fall in blood pressure when it modifies the efficiency of the regulating mechanism, so that it is unable to maintain a reciprocal relationship between peripheral resistance and cardiac output. For this reason, in the whole laboratory animal and in man, it is *usually impossible* to separate the effects on the cardiac output and the effects on the peripheral resistance.

## Clinical Pharmacology of Hexamethonium

### Effect of Hexamethonium on the Blood Pressure and Cardiac Output

*Animal experiments* show no direct effect on perfused hearts but in man the venous pressure decreases after hexamethonium (Restall and Smirk, 1950; Turner, 1950; Burch, 1955), and this may lead [illegible] a fall in the cardiac output. In addition, falls in the right [illegible]

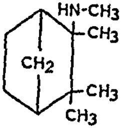
[illegible]

1953). We noted that the decrease in venous pressure preceded the fall of blood pressure (Restall and Smirk, 1950, 1952).

The occurrence of falls in the venous pressure led us [121] to study ballistocardiographic changes with patients in the sitting posture. We found that, judged ballistocardiographically, the cardiac output sometimes increased and sometimes decreased after administration of hexamethonium Patients were then asked to climb about 20 steps, an exercise sufficient, as judged by the ballistocardiogram, to raise the cardiac output above the original baseline level. We found that the increase in the cardiac output with exercise did not prevent the fall of blood pressure with hexamethonium.

Subsequent work, mostly by more exact methods, suggests that the changes in the cardiac output in response to hexamethonium are subject to individual variations, and depend on dosage and other experimental conditions Gilmore et al. (1952), Freis et al. (1952b) and Rakita and Sancetta (1953) reported that the cardiac output was usually but little changed following the administration of hexamethonium and they considered that the fall in blood pressure was due to the decrease in peripheral resistance. In a later report Freis et al. (1953) found that in patients with malignant *hypertension* or heart failure, the cardiac output remained unchanged or increased after

quaternary ammonium compounds of the methonium series. A further communication comes from Stone et al. (1956). It is a highly active substance, causing blockade of the superior cervical ganglion of the cat without interfering with the responses of the nictitating membrane to post-ganglionic stimulation or intravenous adrenaline.



*Mecamylamine*

The blood pressure was reduced in anaesthetized cats. The pressor responses to nicotine and to carotid occlusion were inhibited. The decrease in blood pressure and heart slowing from vagal stimulation were prevented but the responses to injections of adrenaline and acetylcholine were preserved.

The substance does not cause liberation of histamine and has comparatively little blocking action at neuromuscular junctions. Like pentolinium and hexamethonium, it antagonizes the nicotine convulsions in mice, an action suggesting that it has effects upon the central nervous system as well as upon autonomic ganglia. It increases the barbiturate sleeping time in mice.

One of the most interesting differences between mecamylamine and the methonium drugs is that its absorption from the alimentary tract is complete and the dose by subcutaneous injection approximates closely to the oral dose.

## THE CLINICAL PHARMACOLOGY OF GANGLION BLOCKING AGENTS

The falls of blood pressure which result from ganglionic blockade are much less impressive in experimental animals than in man. The reason for this is that the sympathetic nervous system is more important in man, as circulatory adjustments, made necessary by the upright posture, require greater activity of the sympathetic nervous system. In man the effects of hexamethonium in normotension and in hypertension are qualitatively similar but, in most instances, falls of blood pressure are more prominent in hypertensive patients.

Falls in the blood pressure may be brought about either by a decrease in the peripheral resistance or by a decrease in the cardiac output. In

are sometimes substantial but without there being any comparable deviation from the average in the blood pressure level.

## Effect of Hexamethonium on Regional Blood Flow

[illegible] es in the skin temperature was noted by Arnold, [illegible]

and in particular the difference between arms and legs [illegible] is interesting, for Pickering and Hess (1933) and Goetz (1946) showed that there is greater sympathetic vasoconstrictor tone in the lower limbs than in the arms. The greater degree of vasodilatation in the legs than in the arms may be explained by this observation.

Burt and Graham (1950) and R[illegible] (1949) Schnaper et al (1951), usu[illegible] increase in the blood flow through [illegible] methonium The mean blood flow [illegible] from 1 0 ml. to 9 8 ml An increase in the blood flow [illegible] noted with pentamethonium by Crob and Harvey (1950)

When subjects are in the sit[illegible] after hexamethonium, the leg [illegible] same time might [illegible] diminish [illegible] observations) has [illegible] thonium the leg v[illegible] leg volume may take several [illegible] small, but develops rapidly when full blocking doses have been administered; it coincides then with a considerable fall in the blood pressure.

Hamilton, Henley and Morrison (1954) also found that after hexamethonium the changes in blood flow in the hand and forearm were variable, but the only subject who failed to show an increased blood flow in the foot was a hypertensive patient who had previously had a lumbar sympathectomy.

*Portal circulation.* — Freis et al. (1953) made observations on the hepatic portal flow in 5 hypertensive and 2 normal subjects. There was a moderate reduction in the hepatic vascular resistance, but the estimated hepatic portal flow usually decreased. The same authors found a decrease early on in the renal plasma flow, followed by a return to control values, despite continued reduction in the blood pressure level Reynolds et al. (1953) found that following 1 mg./kg. body weight of hexamethonium the estimated splanchnic blood flow by the bromsulphalein method showed a fall, indicating that there was no splanchnic dilatation This was confirmed by a rise in the hepatic arteriovenous oxygen difference.

*Cerebral circulation* — Following the administration of hexamethonium the blood flow through the brain is usually well maintained, according to Crumpton and Murphy (1952) and Stone et al. (1955).

Saunders (1954) pointed out that the effect on cerebral blood flow after hexamethonium depended on whether the patient was horizontal or tilted — head up. Hughes (1955) used a 10 degree foot down tilt and

hexamethonium but in patients with benign essential hypertension, not in heart failure, the cardiac output usually fell. O'Donnell (unpublished observations) found that the cardiac output was not much changed, as an average, in hypertensive patients following hexamethonium. Werkö et al. (1951) noted a fall in the cardiac output in two out of three patients.

Needleman and Horowitz (1953) found an increase in the cardiac output by ballistocardiographic methods in 7 out of 8 subjects on pentamethonium. Palmer (1952) quotes Sharpey-Schaefer and Howard (1949) who say that the cardiac output is reduced when syncope is impending from hexamethonium. Hoobler et al. (1955), using radio iodinated human serum albumin as a tracer substance, determined the cardiac output by the Hamilton-Stewart principle. They found that in acute studies on 5 patients the mean blood pressure fell by 36.7 per cent and the cardiac index by 36.4 per cent. Chronic studies were made in 6 patients after 6 to 128 days' treatment with hexamethonium. The after-treatment values showed a fall of the mean blood pressures of 24.1 per cent and of the cardiac index of 25.9 per cent. They consider, therefore, that blood pressure reduction by ganglion blocking agents (such as pentolinium) is accomplished largely by reduction in the cardiac output.

My impression is that the cardiac output falls in some patients and rises in others. In congestive heart failure it is very likely that the cardiac output rises as the venous pressure falls; and there is a decrease in the peripheral resistance.

The fall in the blood pressure is due primarily to effects on blood vessels, both arteriolar and postarteriolar. In some instances this leads to a decrease in the cardiac output. In the absence of hexamethonium moderate decreases in cardiac output would not be expected to drop the blood pressure much because a compensatory increase in sympathetic tone would lead to an increase of peripheral resistance and, by contraction of veins and venules, to an increase in the return of blood to the heart. Likewise, a decrease in peripheral resistance will only lower the blood pressure when homeostasis is impaired so that a compensatory increase in the cardiac output does not take place. After hexamethonium the blood pressure falls because the nerve pathways maintaining vasomotor tone and subserving these regulatory mechanisms are blockaded. It is, therefore, an oversimplification of the situation in the whole animal to say that the blood pressure falls because the cardiac output or the peripheral resistance is decreased.

An example of effective homeostatic compensation for a decrease in the cardiac output is provided by the absence of a significant fall of blood pressure on the assumption of the erect posture (no hexamethonium), although the cardiac output falls (Gilmore et al., 1952). Differences in the cardiac output between one individual and another

circulation are most conveniently described in conjunction with the effects on excretory processes and are given on page 580. In the meantime it may be stated that most authors consider that soon after hexamethonium is given the renal blood flow decreases, but it recovers again even while the blood pressure remains low.

*Pulmonary circulation.* — There is usually a fall in the pulmonary artery pressure after injections of hexamethonium bromide (Gilmore et al., 1952; Rakita and Sancetta, 1953; Vetter et al., 1954; Storstein and Tueten, 1954; Kilpatrick, 1955; Sancetta, 1955).

Freis et al. (1953) observed a mean decrease in the pulmonary arterial pressure in patients with compensated hearts from 20/14 to 14/8 mm. Hg In the patients with congestive heart failure the pressures fell to an appreciably greater extent. Kelley, Freis and Higgins (1953) noted a decrease in the pulmonary artery pressure after hexamethonium in heart failure cases. Restall and Smirk (1950) noted that during the blood pressure falls, lung congestion diminished, as judged radiographically.

*Various circulatory effects.* — Kelley, Freis and Higgins (1953) found that the arm-to-tongue circulation was increased following the administration of hexamethonium and in 5 out of 11 patients with congestive heart failure there was an increase in the vital capacity.

Hamilton, Henley and Morrison (1954) noted a fall in body temperature after hexamethonium. Finnerty and Freis (1950) also observed a fall of between 1 and 2 degrees Fahrenheit.

The hypotensive action of hexamethonium is enhanced by general anaesthesia according to Davison (1951). Paton and Thompson (1953) studied the action of procaine amide experimentally and found that it appears to potentiate the action of hexamethonium on ganglia in the cat The procaine amide seems to have two actions, one, like hexamethonium, is an inhibition of the action of acetylcholine and the other is an additional effect, the inhibition of acetylcholine release. Mason and Pelmore (1953) found that the combination of procaine and hexamethonium often produced additional falls in the blood pressure level in man. They made use of the combination in controlled hypotension for patients who failed to respond adequately to hexamethonium bromide.

## Effects on Circulatory Homeostasis

We may refer now to a number of procedures, each of which increases the demands for sympathetic activity, i.e., increases the sympathetic load and therefore, as a larger proportion of the blood pressure is neurogenically maintained, the administration of hexamethonium, or of other ganglion blocking agents, causes a larger fall in the blood pressure. Almost all these procedures are influenced by the circulatory adjustments which occur with change in posture and, even in the absence of ganglionic blockade, the simultaneous application of two or

anaesthetized subjects. He found a decrease in cerebral vascular resistance, but a fall in cerebral blood flow. The cerebral oxygen uptake was not significantly altered. Moyer and Morris (1954) obtained similar results in unanaesthetized normotensive subjects in the horizontal posture, and noted that the change in cerebral blood flow was not marked. Saunders (1954) used the horizontal posture with

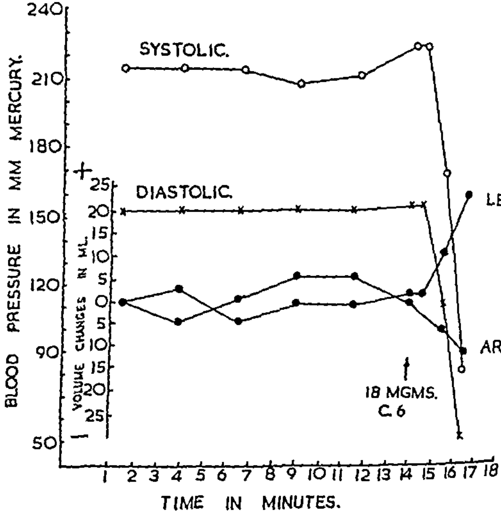



Fig XVIII 4

Effect of hexamethonium on blood pressure and limb volume by plethysmograph The patient was in the sitting posture (Restall, P. A., and Smirk, F. H., Brit Heart J, 14 : 1, 1952).

suction on the legs to increase the blood pressure fall in neurosurgical cases. He took samples of cerebral venous blood, and found the arteriovenous oxygen difference was normal, and the estimated cerebral blood flow (46.9 ml. per 100 gm. of brain a minute) was about equal to that of a normal person.

*Renal circulation.* — The effects of hexamethonium on the renal

blood pressure from hexamethonium and other ganglion blocking agents.

It has long been recognized that the maintenance of the blood pressure level on assumption of the erect posture is dependent upon increased activity of the sympathetic nervous system. When sympathetic activity is decreased by hexamethonium there is a fall of blood pressure which is greatest in the standing posture and least when the patient lies flat (Fig. XVIII 5).

Assumption of the erect posture, is but one of many methods of increasing the load upon the sympathetic system. Whenever the blood pressure level is being maintained homeostatically, thereby increasing the load on the sympathetic nervous system; in other words, when the neurogenically maintained fraction* of the blood pressure is increased, then one may anticipate a larger fall of blood pressure in response to hexamethonium or some other effective ganglion blocking agent.

By way of contrast, another group of procedures, tending for the most part to elevate the blood pressure, cause a homeostatic decrease of sympathetic activity so that the neurogenically maintained fraction of the blood pressure is decreased. These procedures diminish the fall of blood pressure by hexamethonium for there is less neurogenically maintained tone which can be removed by its action.

It will be seen in what follows that there are several procedures which seem to have comparatively little effect upon the circulatory system when the homeostatic regulation is unimpaired. If, however, the demands made on the regulatory system are excessive (sympathetic overloading) or if hexamethonium is used to blockade autonomic nervous responses, then the hitherto concealed effects of these procedures may have striking effects on circulatory dynamics.

*Effects of posture* — Following interference with the activity of the sympathetic system by methonium salts, Arnold and Rosenheim (1949) showed that the blood pressure fall from methonium salts was greatest when the patient was in the standing posture, of an intermediate degree with the patient sitting and least with the patient lying. This effect of posture upon the blood pressure level after hexamethonium has been confirmed by all subsequent workers (Burt and Graham, 1950; Turner, 1950; Finnerty and Freis, 1950; Restall and Smirk, 1950, 1952, May et al. 1951). The extent to which the blood pressure falls in the horizontal posture varies, but in severe hypertensive patients in the standing posture the blood pressure can almost

* The term "neurogenically maintained" fraction of the blood pressure was devised as a means of describing that [illegible] was de- [illegible] ns in the [illegible] of blood [illegible] is given

more procedures, each of which calls for a homeostatic increase of sympathetic activity, may lead to falls of blood pressure due to inability of the sympathetic nervous system to provide an adequate

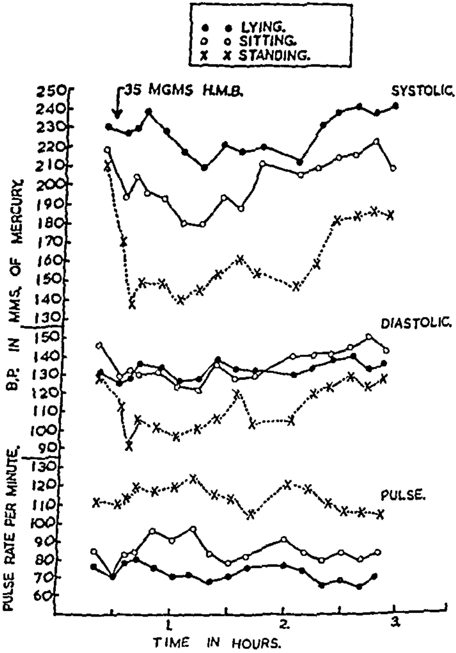



Fig. XVIII 5

Effect of hexamethonium bromide (H.M.B) subcutaneously on the blood pressure and pulse rate in the lying, sitting and standing postures. (Smirk, F. H., and Chapman, O. W., Amer. Heart J., 43 : 586, 1952).

compensatory response. We may speak of this as a state of sympathetic overloading — a condition in which one must expect very large falls of

it was found that, as a hypertensive or normotensive person enters a warm swimming pool and walks towards the deep end, the increasing pressure of the water on the external body surface had no appreciable effect on the arm blood pressure.

After hexamethonium administration, with the blood pressure reduced to hypotensive levels in the standing posture, the response to the swimming bath experiment is altered dramatically (Fig. XVIII 6). As the patient or subject went deeper into the water the blood pressure rose to higher and higher levels until, when the water was up to the chin, the blood pressure was only a little below that recorded before the administration of hexamethonium. The return of the blood pressure, almost to its original high level during immersion, must be due to the counterpressure of the water applied to the external surface of the body, which neutralizes the gravitational increases of intravascular pressure that occur in the lower parts of the body on standing. When after hexamethonium the patient stands erect, but out of the water, this gravitational increase causes distension of blood vessels (arterioles, capillaries and veins) in the lower part of the body, and so a fall of blood pressure results. Gravitational influences involve some sympathetic activity even in the horizontal posture, for even in the horizontal posture the extent of the fall of blood pressure after hexamethonium is reduced if the patient is lowered into a warm bath.

We may draw the conclusion that when a person is immersed in warm water the sympathetic load is reduced — in other words, there is a decrease of the neurogenically maintained fraction of the blood pressure — hence if hexamethonium is administered, the fall of blood pressure is less than it would be with the person in the same posture, but not immersed in water.

These investigations prompted others in which the patient stood in an air pressure chamber with an airtight joint at nipple level. It was found that a positive pressure applied to the body below the level of the nipples would partly counteract the hypotension that develops in the vertical posture after hexamethonium. If, however, the device be used to impose a negative pressure upon the body surface then, in normal and hypertensive people, even in the horizontal posture and without medication, considerable blood pressure reduction [illegible]

[illegible] obtained with mild suction. This principle was applied with great success by our colleague, the late Dr. Saunders (1952), who used a suction device applied to both legs at mid-thigh level as a means of regulating the blood pressure by varying the amount of suction applied to the legs (Fig. XVIII 7). It was found that after hexamethonium it was possible to raise or lower the blood pressure at will by altering the amount of suction applied to the lower limbs. This method

always be reduced to levels such as 80/60 or less by appropriate dosage
Evidently, [illegible]
pressure in [illegible]
were not so hexamethonium would have a comparatively small action.

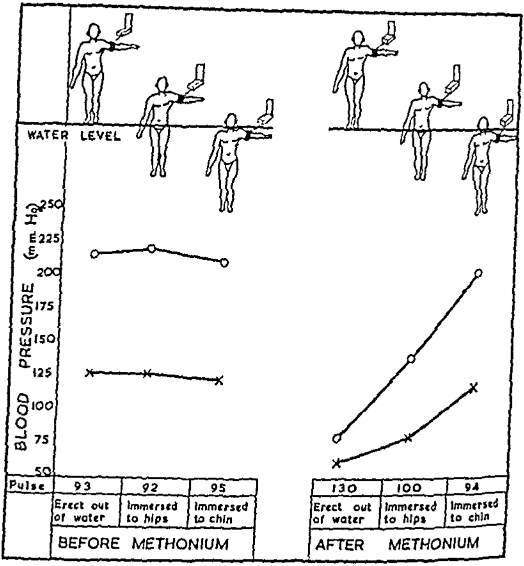



Fig. XVIII 6

Effect upon the blood pressure of immersion of a patient to various depths in water, before and after injection of H.M B. (Restall, P. A , and Smirk, F H , Brit Heart J , 14 . 1, 1952).

*Effect of the application of pressure or suction to the body surface.* — Restall and Smirk (1952) were able to show that the blood pressure changes following assumption of the erect posture were not due to the posture as such but due to the influence of gravity on the distribution of blood and on intravascular pressures. This was done by experiments conducted in a warm swimming pool. In the absence of hexamethonium

it was found that, as a *hypertensive* or normotensive person enters a *warm swimming* pool and walks towards the deep end, the increasing pressure of the water on the external body surface had no *appreciable* effect on the arm blood pressure.

After hexamethonium administration, *with the blood pressure* reduced *to hypotensive levels* in the standing posture, the response to the swimming bath experiment is altered dramatically (Fig. XVIII 6). As the patient or subject went deeper into the water the blood pressure rose to higher and higher levels until, when the water was up to the chin, the blood pressure was only a little below that recorded before the administration of hexamethonium. The return of the blood pressure, almost to its original high level during immersion, must be due to the counterpressure of the water applied to the external surface of the body, which neutralizes the gravitational increases of intravascular pressure *that occur in the lower* parts of the body on standing. When after hexamethonium the patient stands erect, but out of the water, this gravitational increase causes distension of blood vessels (arterioles, capillaries and veins) in the lower part of the body, and so a fall of blood pressure results Gravitational influences involve some sympathetic activity even in the horizontal posture, for even in the horizontal posture the extent of the fall of blood pressure after hexamethonium *is reduced if the patient is lowered into a* warm bath.

We may draw the conclusion that when a person is immersed in warm water the sympathetic load is reduced — in other words, there is a decrease of the neurogenically maintained fraction of the blood pressure — hence if hexamethonium is administered, the fall of blood pressure is less than it would be with the person in the same posture, but not immersed in water

These investiga*tions prompted others in* which the patient stood in an air pressure chamber with an airtight joint at nipple level. It was found that a positive pressure applied to the body below the level of the nipples would partly counteract the hypotension that develops in the vertical posture after hexamethonium If, however, the device be *used* to impose a negative pressure upon the body surface then, in *normal* and hypertensive people, even in the horizontal posture and *without* medication, considerable *blood pressure reductions* occur.

A fall *in* venous pressure occurs concurrently [illegible]

[illegible] success by our colleague, the late Dr Saunders (1952), who used a *suction* device *applied* to *both legs* at mid-thigh level as a means of regulating the *blood* pressure *by* varying the amount of suction applied to the legs (Fig XVIII 7) It was found *that after hexamethonium* it was possible to raise or lower the blood pressure at will by altering the amount of suction applied to the lower limbs. *This method*

of controlling the blood pressure level has been applied in our neurosurgical department by James, Coulter and Saunders (1953) who found that the blood loss during neurosurgical operations could be greatly diminished by the use of hexamethonium in conjunction with negative pressure applied to the legs.



Fig XVIII 7

the device for use in neurosurgery (James, A, Coulter, R L, and Saunders, J W, Lancet, 1 412, 1953)

Such results depend upon the use of hexamethonium to prevent the normal homeostatic circulatory responses to stimuli which, if unopposed, tend to reduce cardiac output or decrease the peripheral resistance

*Venesection.* — The effects of venesection provide an example My colleague O'Donnell (1955) noted that blood donors who had lost one pint of blood showed no significant fall of blood pressure in the horizontal posture but, when tilted to 60 degrees, a moderate postural hypotension was observed (Fig. XVIII 8). A decrease of blood volume requires a homeostatic increase of sympathetic activity and when a further demand is made by assumption of the erect posture there is a degree of sympathetic overloading, and the inability to respond adequately is revealed by the occurrence of postural hypotension. O'Donnell observed, as Freis et al (1951) had reported, that during venesection, the fall of blood pressure after hexamethonium (horizontal posture) was much increased by small blood losses (250 ml.) which

ordinarily do not influence the blood pressure level. Also, the extent of the postural fall with hexamethonium was greatly increased. Restoration of the blood or administration of a blood expanding solution (dextran) restored the postural fall after hexamethonium to its original level (Fig. *XVIII 8*).

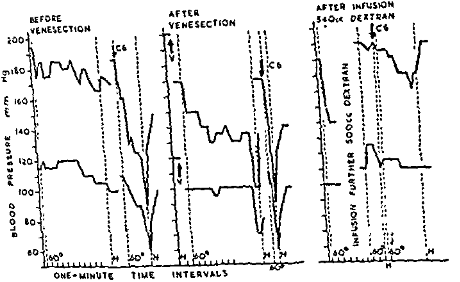



Fig. XVIII 8

The effect of head-up tilt to 60 degrees on an inclined table is studied *before* and *after* venesection. Venesection leads to postural hypotension and a more rapid response to intravenously administered hexamethonium. Restoration of blood volume with dextran solution decreases the postural hypotension as well as the hypotensive action of hexamethonium (O'Donnell, T. V., personal communication)

*Venous congestion of both lower limbs* — Venous congestion of both lower limbs has an effect resembling that of venesection, for while it does not ordinarily influence the blood pressure much, it may be associated with circulatory collapse after hexamethonium (Freis et al., 1951)

*Increase of blood volume.* — The effects noted after venesection led O'Donnell to a study of the effects of blood transfusion and of increasing the blood volume. He noted that the postural hypotension after hexamethonium was diminished if the blood volume of the subject were increased by blood transfusion or infusion of dextran solution. The homeostatic adjustment to an increase in blood volume should involve a decrease in sympathetic nervous action with a decrease in the neurogenically maintained fraction of the blood pressure — hence the decreased response to hexamethonium.

In a number of patients with spontaneous postural hypotension following either neurological lesions, prolonged bed rest or a surgical

procedure, the postural hypotension was greatly lessened by blood transfusion or other methods of expanding the blood volume.

*Salt restriction.* — That salt deprivation is associated with an appreciable increase in the circulatory response to hexamethonium was noted by Restall and Smirk (1950), Freis (1951), Freis et al. (1952), Palmer (1952) Rich and Holubitsky (1953) and Conway (1953). O'Donnell (1955) confirmed these findings and noted that a decrease in the plasma volume had occurred in several of the salt deprived patients. In those patients who exhibited an appreciable fall in the plasma volume the postural fall of blood pressure after hexamethonium was considerably increased, and in some instances a slight degree of postural hypotension was present, even in the absence of hexamethonium. It may be supposed that when severe salt restriction decreases the plasma volume there is a homeostatic increase in the neurogenically maintained fraction of the blood pressure, in that an increase in sympathetic nervous activity is required in order to prevent an appreciable blood pressure fall. As the neurogenically maintained fraction of the blood pressure is increased the effect of hexamethonium is exaggerated and larger blood pressure falls occur in the horizontal posture, and to an even greater extent in the vertical posture, in which posture there is an additional load on the sympathetic nervous system.

These observations of O'Donnell prompted an investigation into the effect of restoring the blood volume in salt depleted patients by an infusion of salt-free dextran solution. In this way the blood volume was restored but the plasma sodium was unaltered or slightly decreased. After restoration of the blood volume the postural hypotension induced by hexamethonium was much diminished, an effect which was evidently not dependent on the concentration of sodium in the plasma. This observation seems to explain, at least in part, the increased activity of ganglion blocking drugs in states of salt deprivation.

*Effect of exercise.* — Probably interference with homeostasis explains the effect of exercise on the action of hexamethonium. When very mild exercise is taken, unlikely to cause much accumulation of metabolites in the lower limbs, the effect of hexamethonium in the standing posture may be diminished, no doubt because the venous pumping effect of muscular action improves the return of blood to the heart. It is well known to most hypertensive patients on hexamethonium that, after moderate or vigorous exercise, standing still may cause faintness. Vasodilatation in the actively exercised muscles from accumulation of metabolites is ordinarily buffered by increased sympathetic activity. Thus, normally after exercise the neurogenically maintained fraction of the blood pressure is increased and therefore a bigger fall of blood pressure occurs if hexamethonium is given.

*Effects of meals, diuretics and purgatives.* — Alstad and I showed in

1951 that following meals, patients who are under the action of methonium salts have an additional fall of blood pressure, presumably due to splanchnic dilatation (Fig. XVIII 9). The same due to u ... action ... 135, 136 ... injection of a mercurial diuretic or had a heavy purgation the effect of hexamethonium was likely to be exaggerated. Though we have no direct evidence, it seems likely that a decrease in blood volume may

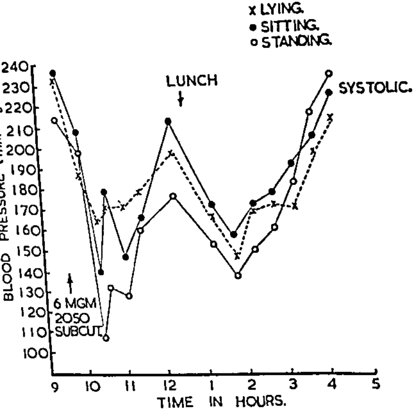



Fig XVIII 9

Effect of 6 mg of subcutaneous pentolinium (Ansolysen) on systolic blood pressure in lying, sitting and standing postures Effect on blood pressure of meal given during action of drug is exemplified (Smirk, F H, Lancet, 1 457, 1953)

have occurred with an increase in the neurogenically maintained fraction of the blood pressure and consequent increase in the reactivity to hexamethonium.

*Effect on other sympathetic reflexes* — It was shown by Finnerty and Freis (1950) that after hexamethonium the reactive rise of blood pressure, which normally follows completion of the Valsalva experiment, no longer occurs. They also noted that the reactionary rise of

blood pressure which normally occurs when a patient is tilted back rapidly from the vertical to the horizontal posture was decreased. A decrease in the reaction to the cold pressor test was also noted by Finnerty and Freis (1950).

*Effect of pressor agents.* — Some procedures tending to elevate the blood pressure have the effect of causing a homeostatic decrease in the neurogenically maintained fraction of the blood pressure. Hypertensives and normotensives after receiving injections of angiotonin, noradrenaline or a synthetic pressor agent S-methyl *iso*-thiourea, were found to exhibit smaller falls of blood pressure after hexamethonium in the horizontal and also in the tilted position (Smirk and Doyle, 1954; Doyle and Black, 1955). It is well known that one of the normal activities of the homeostatic controls is to attempt to buffer blood pressure increases by decreasing the amount of sympathetic activity. Hence, when a pressor agent is given, the increase in the non-neurogenically maintained fraction of the blood pressure is partly offset by a decrease in the neurogenically maintained fraction. Hence the hypotensive action of hexamethonium is diminished, even though the blood pressure is at a higher level at the time when it is administered.

## Effects on Renal Blood Flow and Renal Excretion

In man the estimated renal plasma flow and the glomerular filtration rate are usually decreased temporarily during methonium hypotension (McQueen and Trewin, 1952; MacKinnon, 1952; Haugen and Blegen, 1953; Mills and Moyer, 1953; Freis et al., 1953).

McQueen and Trewin (1952) found that in patients with good renal function the renal plasma flow returns quickly to the original value, even though the blood pressure remains lowered. The effects in patients with greatly impaired renal function were somewhat variable Ford et al (1953) found reduction of the blood pressure with hexamethonium did not lead to any decrease in the renal plasma flow in the horizontal posture. Ullman and Diengott (1953) studied the renal hydrodynamics in two normotensive and 10 hypertensive subjects They found the renal plasma flow and effective renal blood flow were elevated in more than half of the observations and decreased in the remainder The decreases were observed very soon after administration of the drug Mills and Moyer (1953) found that, after hexamethonium intravenously, about half of the subjects showed either no change or a temporary increase in the renal vascular resistance, with a reduction in the glomerular filtration rate and the renal blood flow In the remaining subjects there was a significant decrease in the renal vascular resistance at the time of the maximal blood pressure reduction, so that even then the renal blood flow was maintained near to the control level

It seems to be generally agreed that there is an initial decrease in the volume of urine and delay in the excretion of sodium

McQueen and Trewin (1952) found a decrease in the urine flow associated with a fall in the rate of sodium excretion They noted that the fall in the urine flow

one hour. Ullman and Dengott (1953) also noted a decrease in the urine flow.
Ford et al. (1953) pointed out that in patients under hexamethonium, as well as in control patients, the secretion of urine is much influenced by whether the patient is ambulant or recumbent, the urine volume and sodium excretion being much greater in the recumbent posture.

Usually with continued administration there is no significant delay in renal elimination (Miles et al., 1952; McQueen and Trewin, 1952, Mills and Moyer, 1953) but cases are on record where nitrogen retention has increased during methonium hypotension (Rønnov-Jessen and Bech, 1953; Hayden, 1954).

### Effects on the Alimentary Canal by Blockade of the Parasympathetic Ganglia

Under certain conditions hexamethonium decreases the secretion of hydrochloric acid in the stomach (Kay and Smith, 1950 a, b, 1951; Scott, Kay, O'Hare and Simpson, 1950; Douthwaite and Thorne, 1951). As one would expect, effects depending on the activity of the *secretory nerves to the stomach* are diminished or abolished but chemically stimulated secretion is not prevented.

Kay and Smith (1950a, b; 1951) found that 100 mg hexamethonium intramuscularly inhibited spontaneous secretion in patients with duodenal ulcers and also the secretory response to insulin hypoglycaemia which depends on the [illegible]

[illegible] in duodenal ulcer patients were indefinite They found that 100 mg. of hexamethonium intramuscularly did not produce substantial decreases in the [illegible] of the patients showed achlorhydria. [illegible] marked improvement in some cases of [illegible], however, by a significant reduction in the gastric acidity

Using a balloon method, Kay and Smith (1950a) found a decrease in gastric motility in all of 10 cases of active duodenal ulcer following hexamethonium. The inhibition lasted, as an average, 3 hours 54 minutes after 100 mg of hexamethonium intramuscularly. Kay and Smith (1951) noted that hexamethonium [illegible] in produc- [illegible] Thorne (1950) [illegible] they noted that [illegible]ly caused diminution [illegible]. The duodenum and [illegible] and immobile for periods up to 6 hours after the drug was given. Andrew (1954) also observed a striking inhibition of gastric, duodenal and jejunal motility following the intramuscular administration of 100 mg. of hexamethonium bromide. He

used three balloons placed in the stomach, duodenum and jejunum respectively (Fig. XVIII 10).

We treated a few peptic ulcer patients using subcutaneous injections of hexamethonium but the results were not impressive. In several hypertensive patients with dyspepsia, including proved peptic ulcers, the impression in our clinic was that symptoms were as often aggravated as improved by hexamethonium.

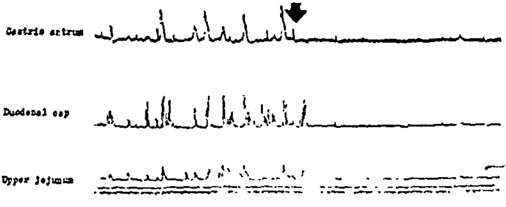



Fig XVIII 10
Hexamethonium bromide (100 mg.) given intramuscularly at arrow. Time interval, 30 seconds. (Andrew, R., Aust Ann. Med., 3 . 305, 1954).

The occurrence of paralytic ileus and other alimentary side effects will be referred to later. Reference will be made also to the occurrence of paralytic ileus in the foetus in cases where the mother is receiving a ganglion blocking drug.

## Absorption, Distribution and Excretion of Methonium Compounds

*Absorption.* — Hexamethonium and its homologues are well known to be much more effective when administered by injection than by mouth. In our experience the ratios of equally hypotensive subcutaneous and oral doses have been of the order of 1:10 or 1:20, and there is a variation from one patient to another in the efficiency of alimentary absorption. Milne and Oleesky (1951) found the urinary excretion of intramuscular hexamethonium was a high proportion of the daily dose injected; but when hexamethonium was administered by mouth the percentage excreted in the urine was 2.3 to 14.6 per cent. They were able to recover some of the hexamethonium from the faeces and concluded that any drug absorbed was excreted quantitatively in the urine. They found that the drug was not affected either by gastric juice or by trypsin.

A valuable study was made by Harington in 1953. He found that, after intravenous administration, the urinary excretion of hexamethonium is rapid and quantitative. When oral doses were given, a

high percentage of the drug was recovered from the faeces, and he was unable to demonstrate any destruction of hexamethonium when it was left in contact with an emulsion of warm faeces. Even in the same patient there was variation from day to day in the extent of the absorption. Harrington found the urinary excretion was commonly less than 10 per cent of the oral doses administered and in hypertensive patients the 24-hour excretion of hexamethonium was found to be 5.4 per cent of the daily dose.

*Distribution.* — It has been pointed out by Höber (1945) that bases usually penetrate cell membranes only when they are in the unionized form and consequently it is to be expected that quaternary nitrogen compounds will be mainly distributed in the extracellular fluids. The observations of Morrison and Paton (1953) suggest that this is the manner in which hexamethonium is distributed in man.

*Excretion* — Young et al. (1951) and Morrison and Paton (1953) found that the renal excretion of hexamethonium resembled that of inulin in that it depended almost entirely on glomerular filtration; thus there is a delay in excretion in cases with impaired renal function. Other reports of delay in excretion of hexamethonium in advanced renal disease come from Milne and Oleesky (1951), Smirk and Alstad (1951) and Harrington (1953).

## Various Effects

*The effect of hexamethonium on insulin hypoglycaemia.* — Insulin

should, therefore, prolong hypoglycaemia but Billington et al. (1954) found that 1 mg /kg of hexamethonium intramuscularly in 12 subjects failed to potentiate the hypoglycaemic action of insulin. They make reference to the papers of Schachter (1952) and of Laurence and Stacey (1952) who consider that the action of insulin is potentiated. Using catheterization of a hepatic vein Reynolds et al. (1953) found no change in the hepatic glucose output following administration of hexamethonium. Likewise the arterial glucose concentration did not change We have made no direct observations in our clinic but have found no decided change in the response to insulin of diabetics who are also under treatment for hypertension with hexamethonium.

*Decrease in sweating* — Decrease in sweating as the result of hexamethonium has been noticed by some of our female patients who have remarked that their skins are much drier and their use of face creams has increased.

*Intraocular pressure.* — Drucker et al. (1950) and Barnett (1952) noted falls in intraocular pressure following the administration of ganglion blocking drugs.

*Drowsiness* — In the early stages of methonium treatment we have

often noted drowsiness. Locket et al. (1951) attributed this to the use of the bromide salt, but this is scarcely reasonable with 15 mg. doses of hexamethonium bromide given subcutaneously. Murphy (1951) points out that drowsiness after hexamethonium is not due entirely to the bromide salt because it occurs with the bitartrate. This has also been our experience.

*Effect on a carotid body chemoreflex.* — An interesting effect of hexamethonium referred to by Hillis and Kelly (1951) is the abolition of the cough which follows an intravenous injection of lobeline, which effect is due apparently to blocking of a carotid body reflex.

*Effect on hiccup.* — From this they concluded that hiccup might be relieved and in a patient with prolonged hiccup they found that this was the case. A previous communication by McGill (1951) referred to a dramatic improvement in a case of hiccup through the administration of hexamethonium.

## Clinical Pharmacology of N,N,N′,N′-3-Pentamethyl-N,N′-Diethyl-3-Aza-Pentane-1,5-Diammonium-dibromide (Pendiomide, Ciba 9295)

The action of Pendiomide in man corresponds closely with that of hexamethonium. Equi-hypotensive initial doses are 17 mg. of Pendiomide and 15 mg. of hexamethonium, but drug toleration develops more rapidly with Pendiomide. It seems to be a less effective hypotensive agent than hexamethonium.

In man, as in animals, the degree to which the blood pressure falls is greater when the blood pressure is high than when it is normal [12, 71], and the falls of blood pressure are much influenced by posture [12, 14]. Decreases in the cardiac output have been observed with large doses [14] but usually the cardiac output is not much altered [12]. Therefore, the fall of blood pressure is described as due mainly to decrease in the peripheral resistance [14]. The heart rate may be increased or decreased a little following intravenous injections of hypotensive doses of Pendiomide [13, 14].

The renal blood flow is somewhat diminished by Pendiomide, there being a degree of decrease in glomerular filtration [27]. Pendiomide also causes a decrease in the output of water and salt [27]. The blood flow through the lower limbs is increased [7]; that of the hands may be increased slightly but not to the same extent.

Blood pressure falls have been reported in essential hypertension and malignant hypertension

Ganglionic blockade with Pendiomide does not interfere with the effect of adrenaline, noradrenaline and ephedrine in man [14] and a clinical trial in a patient with phaeochromocytoma yielded no appreciable fall of blood pressure [71]. The fall of blood pressure was slight in a case of acute nephritis [71].

An interesting effect, which is probably circulatory, is the decrease of the intra-ocular pressure [14, 15].

be expected, parasympathetic blockade gives rise to decrease in the secretion of saliva[14].

## Clinical Pharmacology of Pentolinium
## ([illegible] M. & B. 2050A, Ansolysen)

([illegible]
thonium homolo [illegible] pentolinium [illegible]
1954a, b, 1955a, [illegible]
parison of pento[illegible]
including M. & B. 1950.

Hexamethonium and pentolinium are found to be qualitatively similar but pentolinium is more potent, causes fewer alimentary upsets, and drug toleration does not occur to the same extent on repeated administration.

### Effect of Pentolinium on the Circulation

Like hexamethonium, pentolinium in adequate doses causes falls of blood pressure which are least when the patient is recumbent, of intermediate degree with the patient sitting and greatest with the patient standing (Smirk, 1952a, 1953a, Maxwell and Campbell, 1953, Freis et al., 1954, Birkhead and Allen, 1954, and McMichael and Murphy, 1955).

On assumption of the standing posture the blood pressure does not immediately drop to its lowest level but continues to fall for at least several minutes, provided the patient is standing quietly. Thus, patients who are on doses of pentolinium which leave them quite comfortable when standing immobile for half a minute, may reach hypotensive levels and experience faintness if motionless standing lasts three or four minutes. With large doses the fall to hypotensive levels and onset of faintness may take place rapidly.

When given by subcutaneous or intravenous injection pentolinium is approximately five times as potent as hexamethonium bromide (Smirk, 1952a; Maxwell and Campbell, 1953; Freis et al., 1954). It is of practical importance to recognize that the duration of the blood pressure fall is related to the extent to which the blood pressure is reduced. As with hexamethonium, small falls of blood pressure are usually of short duration, whereas, when the blood pressure of a hypertensive patient (standing posture) is reduced to approximately 120/80 by an injection of aqueous pentolinium, the fall of blood pressure may last from 4 to 6 hours. When doses are used which cause equal falls of blood pressure, the duration of the blood pressure fall induced by pentolinium is more prolonged than that from hexamethonium (Smirk, 1953a, b; Freis et al., 1954; Hale Enderby, 1954). Birkhead and Allen (1954) found no great difference in the duration of effect of hexamethonium

and pentolinium but their published results show that the blood pressure falls in their tests were, on the whole, greater in their hexamethonium than in their pentolinium series of test doses.

We noted that, when administered intravenously, the rate at which the blood pressure falls is slower with pentolinium than with hexamethonium as Freis et al. (1954) and Hale Enderby (1954) have reported.

We find in our clinic that in almost all cases the blood pressure, even in the horizontal posture, may be reduced below basal blood pressure levels by pentamethonium, and Grob (1955) found that he was able to reduce the blood pressure to below the sleeping blood pressures under amytal. When use is made of posture, the blood pressure can be reduced to hypotensive levels in practically all cases.

Hoobler (1954) commented on the great individual variation in sensitivity to initial doses of pentolinium. This has been our experience. Moderate falls of blood pressure may be obtained with initial doses of as [illegible]

[illegible]

believe apply equally to all ganglion blocking agents but they have been worked out more fully for hexamethonium. Hale Enderby (1954) referred to the fact that older patients are more sensitive to the hypotensive action of pentolinium. Certainly in patients who are frail or over 70 years of age it is well to start with half of the normal initial subcutaneous dose, 1.5 instead of 3.0 mg., and to give 10 instead of 20 mg. as an initial oral dose. Freis et al. (1954) noted that a salt-poor diet exaggerates the fall of blood pressure, including the postural hypotension. We have noted this also. After meals there is an additional fall of blood pressure (Smirk, 1953a, b; Ashby, O'Neill and Maclean, 1955).

The pulse rate may increase or diminish after pentolinium (Smirk, 1952a, 1953a, b; Maxwell and Campbell, 1953). Hale Enderby (1954), using intravenous administration, found that tachycardia did not occur frequently.

### Effect on the Kidneys

Hershberger (1955) found that pentolinium hypotension is associated with a decrease in glomerular filtration rate and renal blood flow. After a single dose the glomerular filtration rate and renal blood flow returned towards the original level, even when the blood pressure was still reduced. If the infusion of pentolinium was continued the glomerular filtration rate and renal blood flow remained depressed. Hershberger considered such differences as existed between hexamethonium and pentolinium were an expression of the greater potency of pentolinium. Associated with the alterations in renal haemodynamics there was a decrease in the excretion of water and sodium. Very

similar findings have been reported by Ronnov-Jessen (1955) and by Moyer and Hershberger (1956).

## Absorption and Excretion

The trough of the blood pressure fall usually occurs 2 or 3 hours after administering pentolinium on an empty stomach. Absorption of pentolinium is incomplete so that, as with hexamethonium, 10 or 20 times the subcutaneous dose may be needed to produce a corresponding effect by mouth (Smirk, 1952a, 1953a, b; Maxwell and Campbell, 1953; Freis et al., 1954). Most authors agree that oral dosage with pentolinium is more effective than oral dosage with hexamethonium (Maxwell and Campbell, 1953; Smirk, 1953a, b; Freis, 1954; Freis et al., 1954, Smirk, 1954c, Gifford et al., 1954, Agrest and Hoobler, 1955). Freis et al. (1954) consider that pentolinium is absorbed more predictably than hexamethonium. Certainly pentolinium has been successful in inducing blood pressure falls without alimentary intolerance in patients who have either been resistant to oral hexamethonium bitartrate or have experienced prohibitive alimentary symptoms from it (Smirk, 1953a; Maxwell and Campbell, 1953; Allen et al., 1954).

British and New Zealand authors were, from the outset, more confident than American authors that oral pentolinium was a substantial improvement on oral hexamethonium. Indeed, most British and New Zealand authors have been strong in their condemnation of oral hexamethonium It seems likely now that this disagreement is due to the remarkable fact that hexamethonium chloride which is used in the United States is better absorbed than hexamethonium bitartrate, which was used in British countries, though both should be completely ionized. Even so, oral pentolinium (bitartrate) appears to be better than oral hexamethonium chloride Pentolinium is excreted in part by the kidneys and may be detected in the urine.

## Alimentary Effects

Pentolinium usually causes less constipation than hexamethonium (Maxwell and Campbell, 1953; Smirk, 1953a, b; Freis, 1954; Freis et al., 1954, Grob, 1955) Indeed, in some patients the administration of pentolinium regularly causes an increase in bowel action, presumably due to the predominant effect being an inhibition of the sympathetic innervation of the bowel, whereas the drug usually has a stronger action on the parasympathetic ganglia Choa (1954) found 3 out of his 27 patients had an increased bowel activity The increase in bowel action just mentioned is to be distinguished from the diarrhoea which may occur after several days of constipation

## Other Effects

For equal hypotensive action some patients experience more, and

others less, dry mouth with pentolinium than with hexamethonium or other drugs. Pupil dilatation, according to Maxwell and Campbell (1953), is more pronounced with pentolinium than with hexamethonium. Visual blurring, due to interference with the sympathetic and parasympathetic innervation, occurs with pentolinium, as with hexamethonium.

A diminution in libido and potentia has been described by Moyer et al. (1953), Smirk (1953b, 1955a), Freis (1954), Freis et al. (1954) and Agrest and Hoobler (1955).

## Clinical Pharmacology of Chlorisondamine (SU 3088, Ecolid)

The effects of chlorisondamine in man are fundamentally similar to those of pentolinium (Ansolysen). As with other quaternary nitrogen compounds used in hypertension, the dose by mouth greatly exceeds the subcutaneous dose. Grimson et al. (1955) found chlorisondamine more potent than pentolinium. It resembled pentolinium and hexamethonium by causing postural hypotension, dilatation of the pupils and blurring of vision, dry mouth, decreased force of micturition and constipation. Grimson and his co-workers demonstrated delay in emptying of the stomach after oral doses of 100 mg. The duration of action of chlorisondamine was longer than that of pentolinium and hexamethonium, and Grimson's patients have preferred chlorisondamine to hexamethonium. Smith and Hoobler (1956) obtained rather better results with chlorisondamine than with pentolinium. In their experience constipation was less severe but pupillary dilatation greater.

Observations by Smirk and Hamilton (1955, 1956) on 42 hypertensive patients, 23 having no previous treatment, confirm the observations of Grimson. We compared the relative potency of chlorisondamine and pentolinium. Ordinarily chlorisondamine was 2.1 times as potent as pentolinium for equivalent hypotensive action. Comparisons of the potency of parenteral and oral chlorisondamine indicate that approximately 15 times the parenteral dose must be administered by mouth in order to produce a similar fall in blood pressure. We found that, as with hexamethonium and pentolinium, the duration of the blood pressure fall depended on the extent of the fall. Comparing the duration of action of doses sufficient to reduce the systolic blood pressure in the standing posture to 12[illegible] lasted at least 7 hours. [illegible] solving the chlorisonda[illegible] trough of the blood pressure fall usually occurred between 1 and 2 hours after a subcutaneous injection, and a fully effective dose given parenterally before breakfast maintained, in some instances, an adequate fall in blood pressure during most of the day. The heart rate was unchanged in 7 patients, fell slightly in 10 and rose slightly in 11.

An additional fall of blood pressure occurred after meals as with other ganglion blocking agents (Fig. XVIII 11). The phenomena of [illegible] and cross-toleration are referred to later.

[illegible]

by mouth [illegible] ministered by mouth. On the other hand, some patients who had been well controlled on pentolinium and were transferred to chlorisondamine developed an unexplained malaise with chlorisondamine and preferred pentolinium. Constipation has been the most frequent side effect. Our initial experiences included a patient who approached close to paralytic ileus and another patient with a degree of urinary retention.

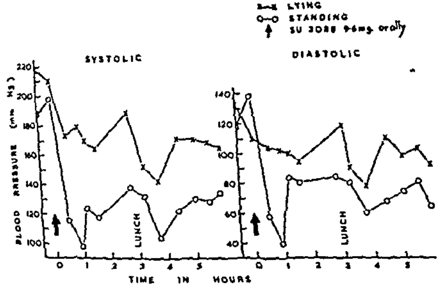



Fig XVIII 11

Response of systolic and diastolic blood pressure to a single oral dose of Ecolid. (Smirk, F. H., and Hamilton, M., Brit. med. J., 1 319, 1956).

Provided no delayed toxic effects emerge, chlorisondamine should prove to be approximately as useful as pentolinium, individual patients doing better on one or the other drug. So far in patients treated for periods up to 4 months the maximum subcutaneous dose used in drug tolerant patients has been 30 mg. and the maximum oral dose 600 mg. in the 24 hours. Maxwell and Howie (1956) had similar experiences as regards dosage requirements. Winsor (1955) found autonomic blockade was frequently obtained in man with oral doses of 200 mg.

## Clinical Pharmacology of 356.C.54 and 139.C.55 (Presidal)

The actions of the two compounds 356.C.54 and 139.C.55 are similar

in many ways but Locket finds 139.C.55, in general, the more satisfactory substance for treating hypertension. The pharmacological effects resemble those of hexamethonium, pentolinium and chlorisondamine qualitatively, blood pressure reduction being associated with inhibition of the parasympathetic system. Locket (1956) found oral dosage inadequate for the treatment of severe cases and he used subcutaneous injection. He commented on blood pressure falls of long duration which made it possible to have twice daily administration of the drug. Blurring of the vision he found was prominent but dryness of the mouth less evident than with some other ganglion blocking drugs. Intestinal propulsion was less affected by 139.C.55 than by pentolinium Nausea and vomiting was not encountered nor severe constipation, though mild constipation occurred.

Our experience has been that effective blood pressure reduction is possible by the oral route but rather more likely to be associated with malaise than corresponding blood pressure reduction by pentolinium. chlorisondamine or mecamylamine. Nevertheless there were individual differences and some patients were more comfortable with oral 139.C.55 (Presidal) than with other drugs. Blurring of the vision was usually complained of but constipation, though encountered, was seldom severe We dispersed papilloedema in two patients with this drug. Our initial experience was with severe cases and some further investigation with this group of compounds seems warranted.

## Clinical Pharmacology of IN 292

We find that blood pressures can be controlled in many severe hypertensive patients by the oral use of IN 292. The taste is objectionable to some patients. Its actions in hypertensive patients resemble those of hexamethonium and pentolinium which is remarkable in view of the evidence that the site of action is predominantly in the central nervous system.

## Clinical Pharmacology of Mecamylamine (Inversine)

There are two remarkable facts about mecamylamine which distinguish it from other hexamethonium analogues.

1. Although it is a secondary amine, its actions after absorption resemble closely those of other ganglion blocking drugs.

2. Unlike the ganglion blocking drugs with a quaternary nitrogen, it is completely absorbed from the alimentary tract and the oral dose is approximately the same as the subcutaneous dose (Moyer et al., 1955; Ford et al., 1955; Freis and Wilson, 1955; Smirk and McQueen, 1956). Zawoiski et al. (1956) have shown that its absorption is intestinal and little if any mecamylamine is absorbed from gastric pouches in dogs. Up to January 1957, it is evidently the most potent of ganglion block-

ing agents and its action is the most prolonged (Moyer et al., 1955; [illegible] 1955; Freis and Wilson, 1955; Smirk and McQueen, [illegible]

[illegible]

therefore unselective in its action and does not discriminate between [illegible] sympathetic ganglia

[illegible] the régime of treatment [illegible]

ganglion blocking agents and, as far as we can make out, all of the side effects occur. A point of great interest is to compare the drug with pentolinium which certainly in recent times has been the drug of choice. The action of mecamylamine is of longer duration and blood [illegible]ntly. The [illegible] the day [illegible]ss capricious than with oral quaternary compounds as absorption from the alimentary canal should be complete.

Our initial impression is that high dose patients who have trouble with oral pentolinium may be better served by mecamylamine. On the other hand, in the limited experience available to us so far, the side effects of the mecamylamine have been rather prominent in some patients, especially constipation, dryness of the mouth and blurring of the vision. The general impression has been that several patients have not been quite so comfortable on mecamylamine as on pentolinium.

One considerable advantage of mecamylamine is that in cases where ileus develops, continued absorption of the drug held up in the obstructed intestines will not add to the danger. The longer period of action of mecamylamine will make it more difficult to treat cases of overdose. Mecamylamine is a new drug and it will be necessary to remain alert to the possibility of delayed toxic reactions.

Rauwolfia alkaloids can be combined with mecamylamine and this combination is considered by Moyer et al. (1955) to be the most satisfactory means of controlling hypertension as far as can be judged at the present time

The administration of reserpine makes it possible to produce equal [illegible]

[illegible] as they do with other ganglion blocking drugs.

## TOLERATION AND CROSS-TOLERATION AMONG GANGLION BLOCKING DRUGS

The occurrence of drug toleration has added to the inherent technical difficulty of obtaining adequate control over the blood pressure level in hypertensive patients. The need on occasion to change from one ganglion blocking agent to another makes it advisable to bring together the results obtained with the various ganglion blocking drugs.

Drug toleration is an important feature of the action of hexamethonium salts (Smirk, 1950; Smirk and Alstad, 1951; Turner, 1951; Rosenheim, 1952; Blainey, 1952; Rich and Holubitsky, 1953; Harington and Rosenheim, 1954). With hexamethonium toleration develops rapidly, so that if two or three fully effective doses of hexamethonium are administered, a degree of drug toleration is apparent next day. With repeated administration frequent increases of dose are necessary daily, or every few days, for several weeks in order to maintain effective falls of blood pressure. Usually within 2 or 3 months the dose is comparatively stable or may even fall a little.

If the administration of hexamethonium is discontinued, drug toleration is lost, so that after a period of a week or ten days it is wiser to resume dosage at about half the level which obtained before interruption of treatment and if the interruption has been for two or three weeks, dosage should be resumed at about one third of the original level.

A degree of drug toleration seems to be present with repeated administration of all ganglion blocking agents which we have tried in man; thus it is present with pentamethonium, M. & B. 1863, M. & B. 1950, pentolinium, Pendiomide, hexa-pyrrolidinium (M. & B. 2024), Presidal (139.C.55) and chlorisondamine. It is present, to some extent at least, with mecamylamine, a point of some interest as the latter compound is a secondary amine.

Maxwell and Campbell (1953) thought drug toleration developed at least as rapidly with pentolinium as with hexamethonium. Others have reported that drug toleration with pentolinium is much less than with hexamethonium or pentamethonium salts (Smirk, 1952a, 1953a, b, 1954a, 1955a; Freis et al., 1954; Agrest and Hoobler, 1955; McMichael and Murphy, 1955). The time taken for the hypotensive dose of pentolinium to become comparatively stable has been variously estimated as between three and eight weeks. Certainly the time varies from one patient to another.

The subject of cross-toleration is important as the development of new and sometimes better compounds and attempts to avoid side effects, may make it necessary to change from one ganglion blocking agent to another.

When hexamethonium is administered repeatedly, a cross-toleration

is established at the same time to the subsequent administration of pentolinium (Smirk, 1953a, b; Smirk, 1955a). Furthermore, when pentolinium is administered repeatedly a degree of drug toleration develops to hexamethonium (Smirk, 1952a, 1953b). There is also cross-toleration between M. & B. 1863 and hexamethonium and pentamethonium. There is, however, a difference in that cross-toleration is practically complete with hexamethonium, pentamethonium and M. & B. 1863, in the sense that before drug toleration develops the ratio of their activity is 1:1:2, and at all stages during the development of drug toleration, whichever drug is first administered, the relationship between the effective doses remains the same, namely 1:1:2. Thus, with these substances, it was possible at any stage in the development of drug toleration to change from one substance to the appropriate dose of another substance and obtain the same hypotensive action (Smirk, 1952b). The degree of cross-toleration between pentolinium and hexamethonium is, however, incomplete (Smirk, 1952a; Freis et al. 1954). Freis et al. (1954) think that the degree of cross-toleration is very slight indeed between these two substances. Certainly, when toleration has been established to an effective dose of hexamethonium, and a

[illegible]

action.

Recently Smirk and Hamilton (1956) found that toleration developed with the repeated administration of chlorisondamine (Ecolid) and a degree of cross-toleration occurs between chlorisondamine and pentolinium in that if chlorisondamine is administered to people who have had no pentolinium previously, the fall of blood pressure is greater than when it is administered to patients previously treated with pentolinium. Likewise, when chlorisondamine is first administered the subsequent fall in blood pressure from administration of an initial dose of pentolinium is smaller than would be expected in an untreated case. After periods of treatment of 40 days or longer, the increase in the dose of chlorisondamine required to produce the same fall of blood pressure has risen in our experience from twice up to five times, or even ten times, the original dose. We found that cross-toleration could be demonstrated between pentolinium and Presidal (139 C 55).

The question of whether mecamylamine, a secondary amine, exhibits cross-toleration with quaternary ganglion blocking drugs is of great interest. Certainly the degree of toleration and cross-toleration is much less than among the quaternary drugs; indeed, though we have the impression that a slight but definite degree of drug toleration to mecamylamine develops in some patients, we cannot be sure that the changes observed are not the result of a shift in dosage level from some other cause.

The phenomenon of drug toleration is sometimes ascribed to some

reactive change taking place in the sympathetic nervous system as a result of the decrease in its activity by blockade of impulses and not involving parasympathetic phenomena. We have no doubt that in man there is toleration to several parasympathetic actions of ganglion blocking drugs and in the mouse to the mydriatic effect. The lack of any important degree of drug toleration after mecamylamine also makes it difficult to accept the idea that drug toleration to ganglion blocking drugs is a general type of reaction to interference with the activity of the sympathetic nervous system.

## References


1 Adamson, D. W., Billinghurst, J. W., and Green, A. F. New series of ganglion-blocking agents Nature (Lond.), 177: 523, 1956

1a Agrest, A., and Hoobler, S. W. Long-term management of hypertension with pentolinium tartrate (Ansolysen). J. Amer med Ass., 157: 999, 1955.

2 Allen, E. V., Barker, N. W., Hines, E. A., Jr., Kvale, W. F., Shick, R. M., Gifford, R. W., Jr., Estes, J. E., Jr Medical treatment of essential hypertension Proc Mayo Clin., 29. 459, 1954

3 Andrew, R. Gastric and intestinal motility studies with morphine, atropine, hexamethonium bromide and "Banthine". Aust. Ann. Med., 3: 305, 1954

4 Arnold, P., Goetz, R. H., and Rosenheim, M. L. Effect of pentamethonium iodide on the peripheral circulation Lancet, 2: 408, 1949.

5 Arnold, P., and Rosenheim, M. L. Effect of pentamethonium iodide on normal and hypertensive persons Lancet, 2. 321, 1949

6 Ashby, D. W., O'Neill, J., and Maclean, M. C Initial control of hypertension with pentolinium tartrate Lancet, 1: 224, 1955

7 Baikie, A. G., and Smith, J. R. A new ganglion blocking agent: trial of 'Ciba 9295' in man. Preliminary communication, Lancet, 1. 1144, 1952

8 Barlow, R. B., and Ing, H. R Curare-like action of polymethylene bisquaternary ammonium salts Brit J. Pharmacol, 3: 298, 1948

9 Barnett, A. J. Ocular effects of methonium compounds Brit J. Opthal, 36: 593, 1952

10 Bartorelli, C., Carpi, A., and Cavalca, L Potentiation of the pressor action of noradrenaline by hexamethonium, tetraethyl-ammonium, and [illegible]

11 Bein, H [illegible] methy[illegible] 9295), einer ganglionär hemmenden Substanz Experientia (Basel), 6. 351, 1950.

12 Bein, H. J., and Meier, R. Pharmakologische Untersuchungen über Pendiomid eine neuartige Substanz mit ganglienblockierender Wirkung Schweiz med Wschr [illegible]

13 Bernsmeier, A., and Esser, H. [illegible] Substanzen auf den Kreislau[illegible] 248, 1951.

14 Bernsmeier, A., Esser, H., and Lorenz, W Klinisch-experimentelle und therapeutische Beobachtungen mit Pendiomid, einer neuen ganglienblockierenden Substanz. Schweiz. med. Wschr, 81: 452, 1951.

15 Bernsmeier, A., and Pau, H Über den Einfluss der Ganglien-blockade

mit 9295 (Ciba) auf die Kreislauf-regulation und den normalen und erhohten Augeninnendruck. Arztliche Forschung, 7: 11, 1951.

16 BILLINGTON, B P., PATON, A., REYNOLDS, T. B., and SHERLOCK, S. The effect of hexamethonium bromide on the circulatory and metabolic response to insulin hypoglycemia in man. J. Lab. clin. Med., 43: 880, 1954.

17 BIRKHEAD, N. C., and ALLEN, E V. Comparison of effects on hypertension of hexamethonium and pentapyrrolidinium injected subcutaneously. Proc Mayo Clin., 29: 489, 1954.

18 BLAINEY, J. D Hexamethonium compounds in the treatment of hypertension. Lancet, 1: 993, 1952

19 BROWN, G. L., and GRAY, J. A. B. Some effects of nicotine-like substances and their relation to sensory nerve endings. J. Physiol., 107: 306, 1948.

20 BURCH, R R. The effects of intravenous hexamethonium on venous pressure of normotensive and hypertensive patients with and without congestive heart failure. Circulation (N.Y.), 11: 271, 1955.

21 BURN, J. H., and DALE, H H. The action of certain quarternary ammonium bases J Pharmacol, 6: 417, 1915

22 BURT, C. C., and GRAHAM, A. J. P. Pentamethonium and hexamethonium iodide in investigation of peripheral vascular disease and hypertension Brit med J., 1: 455, 1950

23 CAVALLITO, C J, GRAY, A. P., and O'DELL, T. B. Sites of action of some unsymmetric bis-quarternary hypotensive agents Arch. int. Pharmacodyn., 101: 38, 1955

24 CHOA, G. H The treatment of hypertension by "Ansolysen" Bull. Hong Kong Chin med Ass, 6: 23, 1954

25 CONWAY, J Sensitivity of autonomic ganglia to hexamethonium in hypertension Brit med. J, 1: 814, 1953.

26 COON, J M, and ROTHMAN, S The nature of the pilomotor response to acetyl choline, some observations on the pharmacodynamics of the skin J Pharmacol, 68: 301, 1940.

27 CRUM-BROWN, A., and FRASER, T R On the connection between chemical constitution and physiological action; with special reference to the physiological action of the salts of the ammonium bases derived from *strychnia*, brucia, thebaia, codeia, morphia and nicotia. J. Anat. (Lond), 1: 224, 1868.

28 CRUMPTON, C W, and MURPHY, Q R Effects of hexamethonium bromide upon haemodynamics of cerebral and coronary circulation in hypertension J clin Invest, 31: 622, 1952

29 CRUMPTON, C W., ROWE, G C, CAPPS, K T, O'BRIEN, G. S., and MURPHY Q R Effect of hexamethonium bromide on coronary flow, cardiac work and cardiac efficiency Proc Nat Meet. Amer. Fed, Clin. Res. No 25, 1953 Cited Rakita, L, and Sancetta, S. M., Circulation Res., 1: 499, 1953

30 DAVISON, M. H A. Danger of methonium drugs. Brit. med. J, 1: 584, 1951

31 [illegible]

32 [illegible] (Lond), 118: 373, 1952.

33 DOUTHWAITE, A. H, and THORNE, M G. The effects of hexamethonium bromide on the stomach. Brit med J, 1: 111, 1951.

34 DOYLE, A. E., and BLACK, H. Reactivity to pressor agents in hypertension. Circulation (N.Y.), *12*: 974, 1955.

35 DREYER, N. B. Action of hexamethonium (C6) on intestine, gall bladder and urinary bladder. Gastroenterology, *26*: 765, 1954.

36 DRUCKER, A. P., SADOVE, M. S., and UNNA, K. R. Ocular manifestations of intravenous tetraethyl ammonium chloride in man. Amer. J. Ophthal., *33*: 1564, 1950.

37 ENDERBY, G. E. H. Pentolinium tartrate in controlled hypotension. Lancet, *2*: 1097, 1954.

38 FASTIER, F. N., BLACKMAN, J. G., PATEL, C. M., and WONG, L. C. K Assessment of depressor activity and mydriatic activity of hexamethonium analogues. Brit. J. Pharmacol., *11*: 282, 1956.

39 FELDBERG, W. Effects of ganglion-blocking substances on small intestine. J. Physiol., (Lond.) *113*: 483, 1951.

40 FINNERTY, F. A., Jr., and FREIS, E. D. Experimental and clinical evaluation in man of hexamethonium (C6), a new ganglion blocking agent. Circulation (N.Y.), *2*: 828, 1950.

41 FORD, R., DENNIS, E., and MOYER, J. H. Pharmacology of mecamylamine (Inversine). J. Lab. clin. Med., *46*: 815, 1955.

42 FORD, R. V., MOYER, J. H., and SPURR, C. L. Hexamethonium in chronic treatment of hypertension — its effect on renal hemodynamics and on the excretion of water and electrolytes. J. clin. Invest., *32*. 1133, 1953

43 FREIS, E. D., Veratrum viride and hexamethonium in the treatment of severe diastolic hypertension Med Ann. Distr. Columbia, *20*: 297, 1951.

44 FREIS, E. D. Recent developments in the treatment of hypertension. Med. Clin. N. Amer., *38*: 363, 1954.

45 FREIS, E. D., FINNERTY, F. A., Jr., SCHNAPER, H W., and JOHNSON, R. L. The treatment of hypertension with hexamethonium. Circulation (N.Y.), *5*: 20, 1952a.

46 FREIS, E. D., PARTENOPE, E. A., LILIENFIELD, L. S., and ROSE, J. C. A clinical appraisal of pentapyrrolidinium (M & B 2050) in hypertensive patients Circulation (N Y.), *9*: 540, 1954

47 FREIS, E. D., ROSE, J. C., HIGGINS, T F, KELLEY, R. T., SCHNAPER, H. W., and JOHNSON, R. L. The hemodynamic effects of hexamethonium in man. (Abstract) J. clin Invest., *31*: 629, 1952.

48 FREIS, E. D., ROSE, J. C., PARTENOPE, E. A., HIGGINS, T F., KELLEY, R. T., SCHNAPER, H W, and JOHNSON, R L The hemodynamic effects of hypotensive drugs in man III. Hexamethonium J. clin Invest., *32*: 1285, 1953

49 FREIS, E. D., STANTON, J R, FINNER [illegible] H. W. JOHNSON, R. L., RATH, C E, an [illegible] produced by venous congestion of [illegible] following certain hypotensive agents J clin Invest, *30*: 435, 1951.

50 FREIS, E. D., and WILSON, I. M. Effects of mecamylamine in hypertensive patients Circulation (N Y ), *12*: 707, 1955

51 GALLAGHER, D. J A A medium for perfusion of innervated blood vessels Brit. J. Pharmacol, *9*: 129, 1954a.

52 GALLAGHER, D. J. A Unpublished observations, 1954b.

53 GIFFORD, R W, ALLEN, E V, and BIRKHEAD, N C. Pentapyrrolidinium bitartrate (M. & B. 2050A) in the treatment of hypertension preliminary observations Proc. Mayo Clin, *29*: 496, 1954

54 GILMORE, H. R., KOPELMAN, H, MCMICHAEL, J., and MILNE, I. G. The

effect of hexamethonium bromide on the cardiac output and pulmonary circulation. Lancet, 2: 898, 1952.

55 GOETZ, R. H. The rate and control of the blood flow through the skin of the lower extremities. Amer. Heart J., 31: 146, 1946.

56 GRIMSON, K. S., TARAZI, A. K., and FRAZER, J. W., Jr. A new orally active quaternary ammonium, ganglion blocking drug capable of reducing blood pressure, Su-3088. Circulation (N.Y.), 11: 733, 1955.

57 GROB, D. Management of the patient with primary essential hypertension. J. Chronic Dis., 1: 546, 1955.

58 GRO[illegible] on the effects of the autonom-[illegible]

Bull. Johns Hopk. Hosp., 87: [illegible]

59 HAMILTON, M., HENLEY, K. S., and MORRISON, B. Changes in peripheral circulation and body temperature after hexamethonium bromide. Clin. Sci., 13: 225, 1954.

60 HARINGTON, M. The absorption and excretion of hexamethonium salts. Clin. Sci., 12: 185, 1953.

61 HARINGTON, M., and ROSENHEIM, M. L. Hexamethonium in the treatment of hypertension. Lancet, 1: 7, 1954.

62 HAUGEN, H. N., and BLEGEN, E. M. The renal response to hexamethonium. Scand. J. clin. Lab. Invest., 5: 58, 1953.

63 HAYDEN, J. G. Treatment of hypertension. Med. J. Aust., 1: 693, 1954.

64 HERSHBERGER, R. L. Renal hemodynamic response to pentapyrrolidinium: comparison with hexamethonium. Amer. J. Med., 19: 142, 1955.

65 HILLES, B. R., and KELLY, J. C. C. Hiccup and hexamethonium. Brit. med. J., 1: 1143, 1951.

66 HÖBER, R. Physical chemistry of cells and tissues. J. & A. Churchill Ltd., London, 1945.

67 HOOBLER, S. W. The modern treatment of hypertension. Bull. Amer. Soc. [illegible] 1951

68 HOOB[illegible]

69 HOO[illegible]

posture. Brit. J. Anaesth., 27: 229, 1955.

70 JAMES, A., COULTER, R. L., and SAUNDERS, J. W. Controlled hypotension in neurosurgery — with special reference to hypotension induced by pneumatic suction applied to the legs. Lancet, 1: 412, 1953.

71 KAISER, F., REICH, E., and SARRE, H. Klinische Erfahrungen mit einem neuen ganglienblockierenden Mittel, Pendiomid. Dtsch. med. Wschr., 76: 1443, 1951.

72 KAY, A. W., and SMITH, A. N. Effect of hexamethonium iodide on gastric secretion and motility. Brit. med. J., 1: 460, 1950a.

73 KAY, A. W., and SMITH, A. N. Effect of oral hexamethonium salts on gastric secretion. Brit. med. J., 2: 807, 1950b.

74 KAY, A. W., and SMITH, A. N. The effect of the ganglion-blocking methonium salts on gastric secretion and motility. Gastroenterology, 18: 503, 1951.

75 KEELE, C. A. Personal communication. Cited by Zaimis, E. J. Acta neuroveg. (Wien), 7: 115, 1953.

76 KELLEY, R. T., FREIS, E. D., and HIGGINS, T. F. The effects of hexame-

thonium on certain manifestations of congestive heart failure. Circulation (N.Y.), 7: 169, 1953.
77 KILPATRICK, J. A. Personal communication.
78 LAURENCE, D. R., and STACEY, R. S. Hypoglycaemia masked by methonium. Lancet, 2: 1145, 1951.
79 LAURENCE, D. R., and STACEY, R. S. Effect of hexamethonium on the response to Insulin in animals and man. Brit. J. Pharmacol., 7: 255, 1952.
80 LIBMAN, D. D., PAIN, D. L. and SLACK, R. Some bisquaternary salts J. Chem. Soc., 430: 2305, 1952.
81 LOCKET, S., SWANN, P. G., and GRIEVE, W. S. M. Methonium compounds in the treatment of hypertension. Brit. med. J., 1: 778, 1951.
82 MCGILL, R. J. Hiccup and hexamethonium. Brit. med. J., 1: 948, 1951
83 MACKINNON, J. Effect of hypotension-producing drugs on the renal circulation. Lancet, 2: 12, 1952.
84 MCMICHAEL, J., and MURPHY, E. A. Methonium treatment of severe and malignant hypertension. J. Chronic Dis., 1: 527, 1955.
85 MCQUEEN, E. G., and TREWIN, E. Hexamethonium bromide and kidney function. Med. J. Aust., 1: 769, 1952.
86 MASON, A. A., and PELMORE, J F. Combined use of hexamethonium bromide and procaine amide in controlled hypotension. Brit. med. J, 1: 250, 1953
87 MASON, D. F. J, and WIEN, R. The actions of heterocyclic bisquarternary compounds, especially of a pyrrolidinium series Brit. J. Pharmacol., 10: 124, 1955.
87a MAXWELL, R. A, PLUMMER, A J, and OSBORNE, M. W. Studies with the ganglionic blocking agent, chlorisondamine chloride in unanesthetized and anesthetized dogs Circulation Research, 4: 276, 1956.
88 MAXWELL, R. D. H., and CAMPBELL, A. J M New sympathicolytic agents. Lancet, 1: 455, 1953.
89 MAXWELL, R. D H, and HOWIE, T. J. G Ecolid a new hypotensive agent. Brit. med, J., 2: 1189, 1955.
90 MAY, E, LAMOTTE-BARRILLON, DUBRISAY, J., and HEYBLON, R. Note préliminaire sur l'emploi des méthoniums chez les hypertendus. Bull. Soc méd Hôp Paris, 67: 440, 1951
91 MILES, B. E, DE WARDENER, H E., CHURCHILL-DAVIDSON, H. C, and WYLIE, W. D The effect on the renal circulation of pentamethonium bromide during anaesthesia. Clin Sci, 11: 73, 1952
92 MILLS, L C, and MOYER, J H The acute effects of hexamethonium on renal hemodynamics in normotensive and hypertensive human subjects. Amer J med Sci., 226: 1, 1953
93 MILNE, G. E., and OLEESKY, S Excretion of the methonium compounds Lancet, 1: 889, 1951.
94 MOHANTY, J K The development of tolerance and cross-tolerance to methonium compounds in laboratory animals Brit. J. Pharmacol, 10: 279, 1955
95 MORRISON, B., and PATON, W D M Unpublished Cited Paton, W D M. and Zaimis, E J Pharm Rev. 4 219, 1952
96 MORRISON, B, and PATON, W. D M. Effects of hexamethonium on normal individuals in relation to its concentration in the plasma. Brit. med J, 1: 1299, 1953.
96a MOYER, J. H., and HERSHBERGER, R. L. The effect of pentolinium on renal hemodynamics and water and electrolyte excretion: A comparison with hexamethonium Amer. J. med. Sci., 231: 294, 1956
97 MOYER, J. H., MCCONN, R, and MORRIS, G. C. Effect of controlled hypo-

tension with pendiomid (as used in surgery) on renal hemodynamics and water and electrolyte excretion — a comparison with hexamethonium and arfonad and the effect of norepinephrine on these responses. Anesthesiology, 16: 335, 1955.

98 MOYER, J. H., and MILLS, L. C. Hexamethonium — its effect on glomerular filtration rate, maximal tubular function, and renal excretion of electrolytes. J. clin. Invest., 32: 172, 1953.

99 MOYER, J. H., and MORRIS, G. Cerebral hemodynamics during controlled hypotension induced by the continuous infusion of ganglionic blocking agents (hexamethonium, pendiomide, and arfonad). J. clin. Invest., 33: 1081, 1954.

100 MOYER, J. H., SNYDER, H. B., JOHNSON, I., MILLS, L. C., and MILLER, S. I. Results with oral hexamethonium alone and in combination with 1-hydrazinophthalazine (Apresoline) in the therapy of hypertension. Amer. J. med. Sci., 225: 379, 1953.

101 MOYER, J. H., KINARD, S. A., CONNER, P. K., CAPLOVITZ, C., FORD, R., [illegible] therapy of hyper[illegible] cal use of meca[illegible] mbinations with [illegible] Rec. (Houston), 49: 390, 1955.

101a MOYER, J. H., FORD, R., DENNIS, E., and HANDLEY, C. A. Laboratory and clinical observations on mecamylamine as a hypotensive agent. Proc. Soc. exp. Biol. (N.Y.), 90: 402, 1955.

101b MOYER, J. H., DENNIS, E., FORD, R., and CAPLOWITZ, C. Mecamylamine in the therapy of hypertension. Circulation (N.Y.), 12: 751, 1955.

102 MURPHY, E. A. Treatment of hypertension with hexamethonium bromide. Lancet, 2: 809, 1951.

103 MUR[illegible] Proc., 12: 101, 1953.

104 NEEDLEMAN, H. L., and HOROWITZ, O. A comparative study of the effects of three vasodilator drugs, pentamethonium bromide (C-5), Dilatol (SKF-1700-A) and Pendiomide (Ba-9295) on the digital cutaneous blood flow. Amer. J. med. Sci., 226: 104, 1953.

105 O'DONNELL, T. V. Unpublished observations.

106 O'DONNELL, T. V. Variations in postural hypotension with changes in blood volume. Proc. Univ. Otago med. Sch., 33: 30, 1955.

107 PALMER, A. J. The management of hypertension with hexamethonium bromide. Med. J. Aust., 2: 428, 1952.

108 PATON, W. D. M., and PERRY, W. L. M. Depolarization and transmission block in the cat's superior cervical ganglion. J. Physiol. (Lond.), 112: 48, 1951a.

109 PATON, W. D. M., and PERRY, W. L. M. The relationship between depolarization and the action potential complex of the cat's superior cervical ganglion. J. Physiol. (Lond.), 114: 47, 1951b.

110 PATON, W. D. M., and THOMPSON, J. W. Procaine amide. Brit. med. J., 1: 991, 1953.

111 PAT[illegible]

112 PAT[illegible] (Lond.), 162: 810, 1948b.

113 PATON, W. D. M., and ZAIMIS, E. J. The pharmacological actions of

polymethylene bis-trimethylammonium salts. Brit. J. Pharmacol., 4: 381, 1949.

114 PATON, W. D. M., and ZAIMIS, E. J. Paralysis of autonomic ganglia by methonium salts. Brit. J. Pharmacol., 6: 155, 1951.

115 PATON, W. D. M., and ZAIMIS, E. J. The methonium compounds. Pharmacol. Rev., 4: 219, 1952.

116 PICKERING, G. W., and HESS, W. Vasodilation in the hands and feet in response to warming the body. Clin. Sci., 1: 213, 1933.

117 PLUMMER, A. J., TRAPOLD, J. H., SCHNEIDER, J. A., MAXWELL, R. A., and EARL, A. E. Ganglionic blockade by a new bisquarternary series, including chlorisondamine dimethochloride (Su-3088). J. Pharmacol., 115: 172, 1955.

118 POOLE, E. W. Reactions of the cat pial circulation to hypotensive states induced by hexamethonium bromide. Arch. Neurol. Psychiat. (Chicago), 71: 640, 1954.

119 RAKITA, L., and SANCETTA, S. M. Acute hemodynamic effects of hexamethonium in normotensive man. Circulation Res., 1: 499, 1953.

120 REDISCH, W., WERTHEIMER, L., DELISLE, C., and STEELE, J. M. Comparison of visceral and peripheral vascular beds in hypertensive patients (Their responses to various "hypotensive" drugs). Circulation (N.Y.), 9: 63, 1954.

121 RESTALL, P. A., and SMIRK, F. H. The treatment of high blood pressure with hexamethonium iodide. N. Z. med. J., 49: 206, 1950.

122 RESTALL, P. A., and SMIRK, F. H. Regulation of blood pressure levels by hexamethonium bromide and mechanical devices. Brit. Heart J., 14: 1, 1952.

123 REYNOLDS, T. B., PATON, A., FREEMAN, M., HOWARD, F., and SHERLOCK, S. The effect of hexamethonium bromide on splanchnic blood flow, oxygen consumption and glucose output in man. J. clin. Invest., 32: 793, 1953.

124 RICH, C. B., and HOLUBITSKY, W. H. The treatment of hypertension with oral hexamethonium. Canad. med. Ass. J., 68. 342, 1953.

124a RØNNOV-JESSEN, V. Pentapyrrolidinium and kidney function. Scand. J. Clin. lab. Invest., 7: 160, 1955

125 RØNNOV-JESSEN, V., and BECH, V. Medicamentel behandlung af hypertensio artenalisforeløbig meddelelse om egne erfaringer med hexamethonium. Ugeskr. Laeg., 115: 589, 1953

126 ROSENHEIM, M. L., Discussion on the medical treatment of hypertension. Proc. roy. Soc. Med., 45: 269, 1952.

127 SANCETTA, S. M. Acute hemodynamic effects of hexamethonium (C6) in patients with emphysematous pulmonary hypertension. Amer. Heart J., 49: 501, 1955

128 SAUNDERS, J. W. Negative pressure device for controlled hypotension during surgical operations. Lancet, 1. 1286, 1952.

129 SAUNDERS, J. W. Effect of controlled hypotension on cerebral function and circulation, Lancet, 1: 1156, 1954.

130 SCHACHTER, M. Hexamethonium and insulin hypoglycaemia. J. Physiol. (Lond.), 115: 206, 1952.

131 SCHNAPER, H. W., JOHNSON, R. L., TUOHY, E. B., and FREIS, E. D. The effect of hexamethonium as compared to procaine or metycaine lumbar block on the blood flow to the foot of normal subjects. J. clin. Invest., 30: 786, 1951.

132 SCOTT, L. D. W., KAY, A. W., O'HARE, M. M., and SIMPSON, J. A. Hexamethonium bromide in duodenal ulcer. Brit. med. J., 2: 1470, 1950.

133 SMIRK, F. H. Practical details of the methonium *treatment of high blood* pressure. N. Z. med. J., 49: 637, 1950.

134 SMIRK F H Effects of hexamethonium bromide homologues in man. [illegible] 1952a.

135 SMIR[illegible] 1952b.

136 SMIRK, F. H. Action of a new methonium compound in arterial hypertension: pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium) bitartrate (M. & B. 2050A). Lancet, 1: 457, 1953a.

137 SMIRK, F. H. *Practical details* of the treatment of hypertension by hexame[illegible] 1 5-bis-N-(*N-methylpyrroli*[illegible]

138 SMIR[illegible]

139 SMIRK, F. H. Il trattamento dell ipertensione [illegible] pentametilene 1,5-bis-N-(N-Metilpirrolidinio) bitartrato. Athena, 6: 1, 1954a.

140 SMIRK, F. H. Results of methonium treatment of hypertensive patients. *Brit med. J.*, 1. 717, 1954c.

141 SMIRK, F. H. Hypertoniebehandlung mit *Hexamethylammoniumsalzen* und Pentamethylen 1,5-bis-N-(N-methyl-pyrrolidinium) bitartrat (M.u B. 2050 A) Die Medizinische, 14. 485, 1955a.

142 SMIRK, F. H. Antihypertensive drugs. Ann. Rev. Med, 6: 270, 1955b.

143 Smirk, F. H, and McQUEEN, E. G. In press.

144 SMIRK, F H, and ALSTAD, K. S. Treatment of arterial hypertension by penta- and hexamethonium salts based on 150 tests on hypertensives of varied aetiology and 53 patients treated *for periods of two to fourteen* months Brit. med J, 1: 1217, 1951.

145 SMIRK, F. H, and DOYLE, A. E. *Neurogenic and humoral factors* in hypertension. Proc Univ. Otago med. Sch, *32: 11, 1954.*

146 SMIRK, F H, and HAMILTON, M. Hypotensive action of N-methyl N-[2'-trimethyl-amino] ethyl 4, 5, 6, 7-tetrachloro*iso*-indoline dichloride. Proc Univ Otago med Sch, 33: 11, 1955

147 SMIRK, F. H, and HAMILTON, M. Action of "Ecolid" in man. Brit. med. J., 1: 319, 1956.

147a STONE, C. A., TORCHIANA, M. L, O'NEILL, G. Q, and BEYER, K. H. Ganglionic *blocking properties* of 3-methylaminoisocamphane hydrochloride (mecamylamine). J. Pharmacol, 116: 54, 1956.

147b STONE, H H, MACKRELL, T. N., and WECHSLER, R. L. *The effect on* cerebral circulation and metabolism in man of acute *reduction in blood* pressure by [illegible] head-up tilt. [illegible]

147c STORSTEIN, O, and [illegible] the pulmonary circulation. Scand. J Clin. lab. Med., 6: 169, 1954.

147d SMITH, J R, and *HOOBLER, S. W Clinical* evaluation of chlorisondamine in the *prolonged treatment of hypertension.* Univ. Mich. med. Bull, 22 51, 1956

148 TURNER, R. "Medical sympathectomy" in *hypertension. A clinical* study *of methonium* compounds. Lancet, 2: 353, 1950.

149 TURNER, R. Methonium compounds *in hypertension. Letter* to Editor, Lancet, 1: 408, 1951.

150 ULLMAN, T D., and DIENGOTT, D. Effect of hexamethonium (C6) on renal hemodynamics in man. Arch. intern. Med., 92: 228, 1953

149a VETTER, H., GRAVNER, G., MLCZOCH, F., and STEINBEREITHNER, K. Herzkatheteruntersuchungen bei massiver Blutdrucksenkung durch Hexamethonium. Klin. Wschr., 32: 7, 1954.

151 WAUD, R. A., LANSING, A. M., and LEWIS, R. A. The effects of veratrum dibenzyline and hexamethonium. J. Pharmacol., 114: 271, 1955.

152 WERKÖ, L., FRISK, A. R., WADE, G., and ELIASCH, H. Effect of hexamethonium bromide in arterial hypertension. Lancet, 2: 470, 1951.

153 WIEN, R. Relation of chemical structure of compounds to their action on autonomic ganglia. Arch. int. Pharmacodyn., 97: 395, 1954a.

154 WIEN, R. Actions of a pyrrolidinium series of compounds. J. Pharmacol., 110: 53, 1954b.

155 WIEN, R., and MASON, D. F. J. Some actions of hexamethonium and certain homologues. Brit. J. Pharmacol., 6: 611, 1951.

156 WIEN, R., and MASON, D. F. J. Personal communication, 1952.

157 WIEN, R., and MASON, D. F. J., Pharmacology of M. & B 2050. Lancet, 1: 454, 1953a.

158 WIEN, R., and MASON, D. F. J. The pharmacological actions of a series of phenyl alkane p-ω-bis (trialkylammonium) compounds. Brit. J. Pharmacol., 8: 306, 1953b.

159 WIEN, R., MASON, D. F. J., EDGE, N. D., and LANGSTON, G. T. The ganglion blocking properties of homologous compounds in the methonium series. Brit. J. Pharmacol., 7: 534, 1952.

159a WINSOR, T. The comparative effects of four ganglionic blocking agents on the cardiovascular system of man. Amer. J. med. Sci., 230: 133, 1955.

160 YOUNG, I. M., DE WARDENER, H. E., and MILES, B. E. Mechanism of the renal excretion of methonium compounds. Brit. med. J., 2: 1500, 1951.

161 ZAIMIS, E. J. The synthesis of methonium compounds, their isolation from urine, and their photometric determination. Brit. J. Pharmacol., 5: 424, 1950.

162 ZAWOISKI, E. J., BAER, J. E., BRAUNSCHWEIG, L. W., PAULSON, S. F., and SHERMER, A. Gastrointestinal secretion and absorption of 3-methylaminoisocamphane hydrochloride (Mecamylamine). Fed. Proc., 15: 205, 1956.

CHAPTER XIX

# TREATMENT OF PATIENTS BY GANGLION BLOCKING AGENTS

## SELECTION OF PATIENTS FOR TREATMENT BY GANGLION BLOCKING DRUGS

[illegible] which determines which patients will be [illegible] treatment should be undertaken.

Physicians who find the response to Rauwolfia alkaloids inadequate turn to more powerful drugs. Those who favour the use of veratrum alkaloids or adrenolytics usually try them before using ganglion blocking drugs (see Chapter XVI). We have found ganglion blocking drugs more satisfactory.

### Strong Indications for Treatment by Ganglion Blocking Drugs

*Non-uraemic patients with malignant hypertension (with papilloedema)* — Almost all authors agree on this[6, 62, 71, 78, 91, 96].

*Patients with hypertensive heart failure or hypertensive cardiac asthma.* — Here we do not place any age limit on patients treated and have seen striking improvements in patients over 70, but results show that the greatest expectation of benefit is with very high pressures and patients under 55. Graham and Maxwell (1954) and Shirley Smith et al. (1954) also regard heart failure and cardiac asthma as cardinal indications of the need for active therapy.

*Patients with grade 3 retinopathy (hard and soft retinal exudates and haemorrhage* [illegible] treatment. [illegible] of treating such patients, as the presence of many exudates in the retina, especially with haematuria, may herald the approach of a malignant phase

*Patients with symptoms and several objective manifestations secondary to hypertension.* — Thus patients whose blood pressures are ordinarily above 200/100, with such manifestations as headache, dizzy attacks, repeated encephalopathy, pulmonary oedema, minor strokes, substantial breathlessness on exertion, palpitation, excessive nose bleeding, are likely to get relief from a régime which lowers the blood pressure levels adequately. The presence of radiological or electrocardiogra-

150a Vetter, H., Gravner, G., Mlczoch, F., and Steinbereithner, K. Herzkatheteruntersuchungen bei massiver Blutdrucksenkung durch Hexamethonium. Klin. Wschr., 32: 7, 1954.

151 Waud, R. A., Lansing, A. M., and Lewis, R. A. The effects of veratrum, dibenzyline and hexamethonium. J. Pharmacol, 114: 271, 1955.

152 Werkö, L., Frisk, A. R., Wade, G, and Eliasch, H. Effect of hexamethonium bromide in arterial hypertension. Lancet, 2: 470, 1951.

153 Wien, R. Relation of chemical structure of compounds to their action on autonomic ganglia. Arch. int. Pharmacodyn., 97: 395, 1954a.

154 Wien, R. Actions of a pyrrolidinium series of compounds. J. Pharmacol, 110: 53, 1954b.

155 Wien, R., and Mason, D. F. J. Some actions of hexamethonium and certain homologues. Brit. J. Pharmacol., 6: 611, 1951.

156 Wien, R., and Mason, D. F. J. Personal communication, 1952

157 Wien, R., and Mason, D. F. J., Pharmacology of M. & B. 2050. Lancet, 1: 454, 1953a.

158 Wien, R., and Mason, D. F. J. The pharmacological actions of a series of phenyl alkane p-ω-bis (trialkylammonium) compounds Brit J.

159 [illegible]
series. Brit. J. Pharmacol, 7: 534, 1952.

159a Winsor, T. The comparative effects of four ganglionic blocking agents on the cardiovascular system of man. Amer. J. med. Sci, 230. 133, 1955

160 Young, I. M, de Wardener, H. E., and Miles, B. E. Mechanism of the renal excretion of methonium compounds. Brit. med. J., 2: 1500, 1951

161 Zaimis, E. J. The synthesis of methonium compounds, their isolation from urine, and their photometric determination. Brit. J. Pharmacol, 5: 424, 1950.

162 Zawoiski, E. J., Baer, J E, Braunschweig, L W., Paulson, S. F, and Shermer, A Gastrointestinal secretion and absorption of 3-methylaminoisocamphane hydrochloride (Mecamylamine). Fed. Proc, 15: 205, 1956

TABLE XIX 1

| *Favouring Treatment by Ganglionic Blockade* | Against Treatment by Ganglionic Blockade |
|---|---|
| 1. Presence of potentially reversible hypertensive manifestations such as breathlessness, substantial headache, giddiness, etc. | Symptomless. |
| 2. Presence of objective hypertensive changes such as enlarged heart, gallop rhythm, electrocardiographic changes, alternans, retinal *grade* 2, 3 or 4 *minor* strokes | No objective changes. |
| 3 Casual blood pressure usually above 210/110. | Casual *blood* pressure usually below 200/100. |
| 4 Ba [illegible] responds approximately with an "amytal" blood pressure). | Basal blood pressure usually *below 150/85* |
| 5. Expectation of *leading* a worthwhile life | Presence of impairments limiting possible *improvement* such as strokes, senility. |
| 6. Presence of teneseness and trouble with aggressive traits. | *Neurotic and a varied collection* of non-hypertensive *complaints; or with* a past history of psychotic illness. |
| 7 *Under* 65 | *Over 65.* |
| 8 Patient is a male | |
| 9 Family history of progressive hypertensive disease at an early age | Family history favourable. |
| 10 Intelligent, *of* stable disposition and attentive to detail | Unintelligent and without intelligent relatives who could *supervise* treatment. |
| *11* Desires to co-operate. | Unenthusiastic and lax. |
| 12. Supervision *of* régime readily arranged. | No adequate medical assistance in patient's neighbourhood. |
| 13. A blood non-protein nitrogen below 50 mg. per cent | A blood non-protein nitrogen above 60 mg. per cent in the absence of heart failure. |

phic evidence of cardiac hypertrophy would strengthen the indication for controlling the blood pressure level.

*Symptomless patients with blood pressures over* 250/140. — These patients have been offered treatment in our clinic irrespective of personality or aetiology. Usually in such patients there is some objective change in the heart size, electrocardiogram or retinae which can provide a measure of the effects of treatment.

As the result of a follow-up study recently completed, it is proposed to accept for treatment symptomless patients with basal blood pressures (see Chapter XII) exceeding 160/95 in males or 175/100 in females. These are high levels for basal pressures. Most such patients would have casual blood pressures exceeding 220/120.

## Patients Requiring Close Consideration

Many patients who do not come into the most severe category derive great benefit from effective treatment and are able to live more [illegible] or unfavourable to successful therapy.

We do not use any score system in reaching a decision but a general indication of our practice in selection may be obtained by allocating one point for the presence of each feature favouring treatment (Table XIX 1). Nearly all our patients accepted for hypotensive therapy in the past would have been expected to score at least 2 and usually 3 or 4 points among the first four features favouring treatment and have a total score of not less than 7, and usually of 8 or more out of a possible 13.

In general, the higher the blood pressure, the more it is fixed (non-labile), and the more prominent are the potentially reversible clinical manifestations arising from it then so much the stronger are the indications for methonium therapy. The chance of dramatic improvement is greater if the patient is young.

## Special Problems

*Angina with high blood pressure.* — We were hesitant at first about [illegible] over 210/105 at clinic visits. Treatment is continued in those patients whose exercise capacity is improved.

*Recent cardiac infarction* is ordinarily a contraindication, but we gave small doses of hexamethonium bromide by injection at about the fifth week after a cardiac infarction in a female patient whose blood pressure, rising again, had led to attacks of cardiac asthma. The

appeared with fall of blood pressure and [illegible]
rose again

## PRINCIPLES OF TREATMENT BY GANGLION BLOCKING DRUGS

Although the use of ganglion blocking agents is advocated as being usually the most satisfactory method of reducing the blood pressure it is desired to emphasize that the reason for preferring ganglion blocking drugs, alone or with Rauwolfia alkaloids, is that in our experience they provide, at the present time, the most satisfactory means of reducing the blood pressure to near normal levels, at least in the trough of the blood pressure fall

Ganglionic blockade is not an ideal method of reducing the blood pressure but the drugs used are effective and, with rare exceptions, the question is not whether the blood pressure can be reduced but how and to what extent it shall be reduced

In our clinical trials with methonium halides and other ganglion blocking agents in over 400 hypertensive patients selected for treatment, we found [71, 84, 85, 86, 91] that with the aid of posture, substantial falls of blood pressure are induced in all the common types of arterial hypertension, viz essential, malignant, in the course of pregnancy toxaemia, following pregnancy toxaemia, in nephritic and other renal types, Cushing's syndrome, aortic coarctation and the type associated with polycythaemia vera In all but four or five out of 400 patients the blood pressure could be lowered to near the normal level by methonium salts combined with the sitting or standing posture. This is not surprising, blockade of normal sympathetic impulses should lower the blood pressure, and in almost all patients with hypertension there is an increase in the neurogenically maintained fraction of the blood pressure (Chapter XI) McMichael (1952), and Green and Ellis (1954) also did not encounter any irreversible cases of hypertension.

Ideally, treatment should be initiated during a stay in hospital or by all-day visits to a hospital clinic or doctor's rooms with a return home at night if transport facilities are adequate. Under these circumstances the changes in the blood pressure induced by ganglion blocking drugs are followed over 3 to 6-hour periods by trained technicians. In the absence of special technicians a nurse, secretary or receptionist can usually be trained to conduct tests. Where technical help is lacking a system of dosage adjustments will be suggested which, though less satisfactory, is easier for private practice or for hospitals without a hypertensive clinic.

cardiac asthma in this patient was alleviated by lowering the blood pressure.

*Emotionally tense hypertensive patients*, over-alert and predisposed to anger, sometimes with trivial provocation, commonly get relief when the blood pressure is reduced by methonium compounds. In several instances this has not depended on the removal of other symptoms, since it has happened in patients who were otherwise symptomless. This sometimes distressing personality trait of many hypertensive patients (see Chapter VII) is an indication for treatment. The relief is sometimes striking and such patients do not return at a later date with a variety of neurotic complaints. On several occasions improvement in temperament has been important to the patient's family. A distinction is drawn between these patients and others who present themselves with neurotic predisposition to aches, pains and queer visceral sensations and whose neuroses are as likely to be aggravated as improved by a detailed régime.

*Psychotic illnesses.* — Patients who have had serious *psychotic illnesses*, even though they have apparently recovered, are often difficult to manage and seem much more likely to discontinue treatment for trivial reasons than most other patients. While this should not prevent treatment being undertaken in severe cases, it can fairly sway the decision in doubtful cases.

*In nephritis*, hypertensive symptoms are alleviated as in other forms of hypertension (Smirk and Alstad, 1951; McMichael, 1952). In most instances the non-protein nitrogen is not elevated further when the blood pressure is reduced. Treatment should be of an exploratory nature until it has been shown that the patient tolerates blood pressure lowering without developing nitrogen retention. The risk of an acute exacerbation, ending in uraemia, persists.

*Cerebral vascular accidents.* — In subarachnoid haemorrhage with a high blood pressure we have used ganglion blocking drugs in several instances with the idea of preventing recurrence of the bleeding, and the results obtained warrant further study.

We are uncertain whether ganglion blocking drugs should be administered in patients who have had a recent cerebral haemorrhage involving the cerebral substance. In some cerebral cases where the diagnosis rested between substantial hypertensive encephalopathy and a minor cerebral thrombosis, we have administered hexamethonium subcutaneously, in the hope that if the former were the correct diagnosis improvement might follow. In some instances a temporary increase in limb or facial weakness followed blood pressure reduction and steps were taken at once to restore the arterial level

An old hemiplegia of mild degree does not contraindicate treatment.

*Patients with menorrhagia and hypertension* frequently get relief from blood pressure lowering. In one of our patients bleeding from uterine

rose again

## PRINCIPLES OF TREATMENT BY GANGLION BLOCKING DRUGS

[illegible] blocking agents is advocated as being [illegible] drugs, alone or with Rauwolfia alkaloids, is [illegible] provide, at the present time, the most satisfactory means of reducing the blood pressure to near normal levels, at least in the trough of the blood pressure fall.

Ganglionic blockade is not an ideal method of reducing the blood pressure but the drugs used are effective and, with rare exceptions, the question is not whether the blood pressure can be reduced but how and to what extent it shall be reduced

In our clinical trials with methonium halides and other ganglion [illegible] over 400 hypertensive patients selected for treat- [illegible] hypertension, viz essential, malignant, in the course of pregnancy toxaemia, following pregnancy toxaemia, in nephritic and other renal types, Cushing's syndrome, aortic coarctation and the type associated with polycythaemia vera In all but four or five out of 400 patients the blood pressure could be lowered to near the normal level by methonium salts combined with the sitting or standing posture. This is not surprising, blockade of normal sympathetic impulses should lower the blood pressure, and in almost all patients with hypertension there is an increase in the neurogenically maintained fraction of the blood pressure (Chapter XI) McMichael (1952), and Green and Ellis (1954) also did not encounter any irreversible cases of hypertension.

Ideally, treatment should be initiated during a stay in hospital or by all-day visits to a hospital clinic or doctor's rooms with a return home at night if transport facilities are adequate. Under these circumstances the changes in the blood pressure induced by ganglion blocking drugs are followed over 3 to 6-hour periods by trained technicians In the absence of special technicians a nurse, secretary or receptionist can usually be trained to conduct tests Where technical help is lacking a system of dosage adjustments will be suggested which, though less satisfactory, is easier for private practice or for hospitals without a hypertensive clinic

## Effect of Posture

The blood pressure fall after administration of ganglion blocking drugs is greatest in the standing posture, less in the sitting posture, and comparatively small in the lying posture (Arnold and Rosenheim, 1949, Burt and Graham, 1950; Restall and Smirk, 1950; Turner, 1950; Saville, 1950; Smirk and Alstad, 1951; Chisholm, 1951; Palmer, 1952). It is now generally agreed that therapeutic use must be made

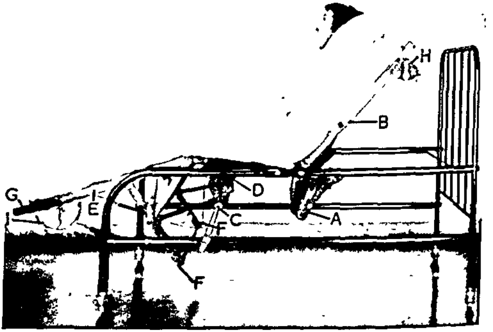



Fig XIX 1a

Cardiac bed as used for hypertensive patients at Dunedin Hospital

Cardiac bed Handle attached at 'A' elevates or lowers the back rest 'B' Handle at 'C' raises the buttock support 'D' ar... ment 'F' operated by lever system 'G... in upward or downward direction Pro... ward inclination of the back rest and downward inclination of the leg rest

of the postural falls of blood pressure (Restall and Smirk, 1950, McMichael, 1952; Rosenheim, 1952, Palmer, 1952, Shirley Smith et al., 1954).

In our clinic we insist that the patient should be either in the sitting or standing posture throughout the day and at night should sleep propped up at an angle of 45 degrees. We use a cardiac bed in hospital (Fig. XIX 1a) and a simple domestic device (Fig XIX 1b) in the home. We are agreeable to an alternative in certain patients, namely, that the head end of the bed should be raised by 12 or 15 inches, preferably 15, the patient lying flat (Fig. XIX 2); but we prefer patients to be propped up at 45 degrees in a sitting position.

When the patient taking the drug is in the sitting or standing posture the doses needed to produce a good fall of blood pressure are smaller, and this is ... 'ose ... to of hexamethonium ... ab- reduce the blood p... normal levels will not be dangerous, because if the patient lies down the blood pressure will be restored to normal or hypertensive levels.

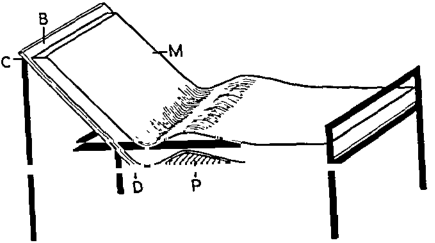



Fig XIX 1b

A simple device for home or hospital use to replace the cardiac bed A back-board CD, usually of 5-ply wood with holes bored at the upper edge is tied at the head of ... ress M rests on the ... eneath the mattres ... end of the mattress ... nd of the knee An ... is to use strong canvas in place of the back-board

On the other hand, if large doses of hexamethonium or other ganglion blocking drugs are administered which cause hypotension in the lying posture, this simple restorative measure is no longer applicable, and also parasympathetic side effects will be much more prominent.

## Reduction of the "Trough" Blood Pressure (Standing) to Normal as the Aim of Treatment

th... XIX 3 have one ... preparation or drug used, the dose employed is the dose which is found to reduce the blood pressure in the trough of the depression to approximately 120 mm. Hg systolic, the pressure being measured with the patient in the standing posture We call this the "trough" blood pressure (standing).

The reason why the blood pressure is measured with the patient

standing is that by doing so the extent of the blood pressure fall can be adjusted to suit an ambulant patient. The dose is adjusted until the extent of the fall is just short of that which would induce faintness in the standing posture. If the patient is confined to bed the dose may be regulated so as to reduce the blood pressure to approximately normal in the trough of the blood pressure fall, the patient being in the sitting posture with a back rest at 45 degrees.

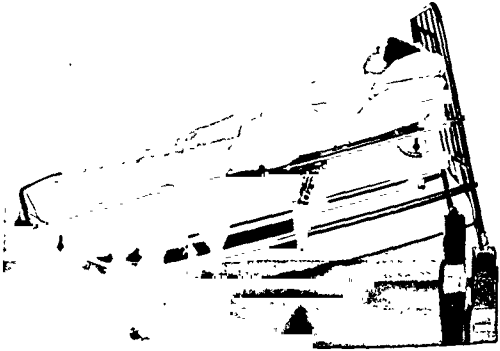


Fig XIX 2

In the few patients who cannot tolerate the sitting posture, the head end of the bed is raised on blocks 16 inches high

In patients who tolerate normal blood pressures without symptoms, the aim should be to keep the blood pressure below 150 systolic in the sitting or standing posture for as much of the day as is possible. This will usually be achieved with long acting drugs if the trough blood pressure (standing) is in the region of 120 systolic Sometimes during initiation of treatment hypotensive symptoms occur before the blood pressure approaches normal levels (for example, at 170/120) but persistence in reducing the blood pressure at each injection, as far as can be done without inducing important symptoms, will improve the patient's tolerance of more normal blood pressures It is not necessary to achieve the maximum effect in the first few days, and on occasion some months have elapsed before nearly normal pressures are tolerated, but, once the patient's reaction to one of these drugs is determined, it

o adjust the dose so that the blood pressure ... g quietly is one which can be tolerated without appreciable symptoms.

## Effect of Drug Toleration

Drug toleration develops with repeated administration (Restall and Smirk, 1950; Smirk and Alstad, 1951; Freis, 1951; McMichael, 1952; Palmer, 1952; Morrison, 1953) so that for a time, perhaps two or three months, in order to maintain the same hypotensive action the amount

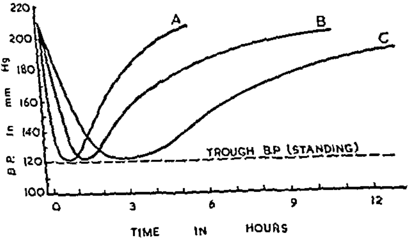



Fig. XIX 3

Lines A, B and C indicate approximately the effects on the blood pressure taken in

17 839, 1954)

of drug injected will have to be increased, daily at first and weekly later. Sometimes the dose is already stable within a month of starting treatment The dose of hexamethonium

...onium drug toleration develops but not usually as much as with hexamethonium. A degree of drug toleration develops with chlorisondamine (SU 3088), but also less than with hexamethonium.

## Relation of Dose to Response

The correct dose is critical in that, if the ideal hypotensive action is produced by a subcutaneous dose of say 100 mg. of hexamethonium then as little as 5 mg., and certainly 10 or 15 mg., below the ideal dose is likely to give too little action; and 5 to 10 mg. above the ideal dose may give an excessive action. The same need for critical adjustment of the dosage level is apparent with M. & B. 1863, pentolinium (Fig. XIX 4) and chlorisondamine. The effects of comparatively small alterations in the dose make a considerable difference also to the patient's

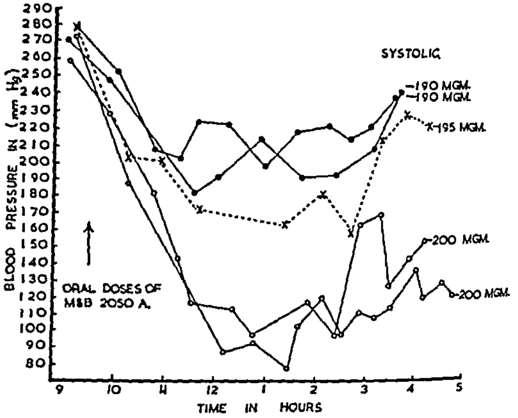



Fig XIX 4

Effect of pentolinium (M. and B 2050 A, Ansolysen) by mouth on the systolic blood pressure in a patient who had a narrow range of therapeutic response, showing the need for accuracy in dosage. (Smirk, F H, Lancet, 1 457, 1953)

comfort. Hence, much effort on the part of the doctor and co-operation from the patient are needed to discover and maintain the correct dosage.

The observations of Morrison and Paton (1953) are of great interest. They found a close relationship between the plasma concentration of hexamethonium and the effects on the blood pressure and they remark that the relationship was unusual in that the effect of the drug varied directly with its concentration in the body rather than with the

TABLE XIX 2. — *Doses of Ganglion Blocking Drugs*

| Drug | Route of Administration | Initial dose (as salt) mg | Usual dose increment mg | Maximum daily dose used in Dunedin Clinic* | Range of dose usually employed after development of drug toleration mgms | Comments |
|---|---|---|---|---|---|---|
| *Hexamethonium* bromide (*H M B*) | *I V* | *5* | *5* | — | — | 5 mg every 2 min until desired effect obtained |
| *Hexamethonium chloride (H M C.)*<br>Hexamethonium bromide (H M B) | subcut. | 15 | 5 | 1200 | *100—500* | no longer applicable for routine therapy |
| *Hexamethonium chloride (H.M C)*<br>Hexamethonium bromide (*H M B*) | oral | 125 | 125 | 5000 | not recommended | undesirable because of *bromism* |
| *Hexamethonium* chloride (H.M C) | *oral* | 125 | 125 | — | — | H.M C. is better absorbed than H M.T. |
| Hexamethonium tartrate (H M.T) | oral | *187* | 187 | 9000 | 1500—3500 | a few patients still *prefer* oral hexa*methonium* to oral pento*linium* |
| *Pentolinium* (Ansolysen) | *I V* | 1 | 1 | — | — | |
| Pentolinium (Ansolysen) | subcut. | 3 | 1—2 | 150 | 20—100 | |
| *Pentolinium* (Ansolysen) | oral | *20* | 10—20 | 1500 | 100—900 | |
| Chlorisondamine chloride (Ecolid) | subcut | 1.5 | *1.5* | insufficient data | 5—30 | |
| Chlorisondamine *chloride (Ecolid)* | oral | 10 | *5—10* | 750 | *60—500* | |
| Mecamylamine *(Inversine)* | oral | 5 | 1—2 | 110 | 10—60 | drug toleration inconspicuous |

* The *maximum daily dose as referred* to in this column is higher than would be recommended ordinarily but in some instances patients have been *maintained on daily* doses not appreciably lower than those in this column.

logarithm of its concentration. Their observation explains, in part, the need for the critical dosage adjustment without which it is impossible in many instances to avoid excessive side effects without undue loss of hypotensive action.

### Initial Doses and Dosage Increments for Ganglion Blocking Drugs

Common to all ganglion blocking drugs is the principle of starting with an initial dose which will be safe and adding a standard dose increment by which the dose level is raised, usually daily until an adequate effect is obtained and then less frequently to keep pace with the development of drug toleration. When mention is made of adding or subtracting a dose increment the reference will be our standard dose increment for the drug as set out in table XIX 2. If the patient has had a sympathectomy, is already on Rauwolfia drugs, or is frail, over 65, on a salt-free diet, or in congestive heart failure the initial doses should be half of the above.

## INFORMATION AS TO THE DEGREE OF CONTROL OVER BLOOD PRESSURE LEVELS

Success with ganglionic blockade or other treatment for high blood pressure depends on forming a correct estimate of the degree of control exercised by the régime over the 24-hour day. Casual blood pressures taken at a clinic are often inadequate for the purpose and may give false indications.

Comments are made below on six ways of evaluating the hypotensive action of drugs; especially ganglion blocking drugs.

1. Three to six hour tests by technicians.
2. The "standing test".
3. By symptoms indicative of drug action.
4. Casual blood pressures.
5. Home blood pressures.
6. Use of tests with placebos.

### (1) Three to Six Hour Tests by Technicians

We have found these tests to be the most reliable guide to the proper dose of a ganglion blocking drug and helpful in reaching decisions concerning the effects on the blood pressure of other forms of therapy.

Unless incapacitated our patients are not admitted to hospital but

attend the technicians' room for about seven hours daily, five days weekly, usually for three weeks. In the absence of research interests the time could be reduced to about once every three or four days, but with less precise control over dosage there might be occasional frights for the patient and establishment of a satisfactory régime would take longer. From the doctor's standpoint there is an enormous advantage while gathering experience, in following the daily changes in the patient's sensitivity to the drug used and in having before him a chart of the blood pressure changes in various postures, together with a note on the relationship between the various symptoms which may occur and the level of the blood pressure at the time.

is confined to bed. Blood pressures for routine control are not measured in the lying posture because our patients on ganglion blocking drugs only adopt the lying posture as a temporary measure to combat the effect of an inadvertent overdose.

During this initial period the patient is provided with typed instructions (see Appendix 1) and difficulties are discussed and explained. It is most important that the patient should understand something of the workings of the drugs, and in our experience the technician is invaluable in educating patients, any special points she cannot answer being dealt with when the doctor comes round or at the outpatient sessions

The few patients who are now on injection treatment are given instructions

sive symptoms occur or if the systolic blood pressure falls below 110 mm in the sitting posture

Where practicable any trial made with veratrum alkaloids should not be conducted in the same room as methonium trials, as the toxic

logarithm of its concentration. Their observation explains [illegible]

hypotensive action.

## Initial Doses and Dosage Increments for Ganglion Blocking Drugs

Common to all ganglion blocking drugs is the principle of starting with an initial dose which will be safe and adding a standard dose increment by which the dose level is raised, usually daily until an adequate effect is obtained and then less frequently to keep pace with the development of drug toleration. When mention is made of adding or subtracting a dose increment the reference will be our standard dose increment for the drug as set out in table XIX 2. If the patient has had a sympathectomy, is already on Rauwolfia drugs, or is frail, over 65, on a salt-free diet, or in congestive heart failure the initial doses should be half of the above.

## INFORMATION AS TO THE DEGREE OF CONTROL OVER BLOOD PRESSURE LEVELS

Success with ganglionic blockade or other treatment for high blood pressure depends on forming a correct estimate of the degree of control exercised by the régime over the 24-hour day. Casual blood pressures taken at a clinic are often inadequate for the purpose and may give false indications.

Comments are made below on six ways of evaluating the hypotensive action of drugs; especially ganglion blocking drugs.

1. Three to six hour tests by technicians.
2. The "standing test".
3. By symptoms indicative of drug action.
4. Casual blood pressures.
5. Home blood pressures.
6. Use of tests with placebos.

### (1) Three to Six Hour Tests by Technicians

We have found these tests to be the most reliable guide to the proper dose of a ganglion blocking drug and helpful in reaching decisions concerning the effects on the blood pressure of other forms of therapy.

Unless incapacitated our patients are not admitted to hospital but

attend the technicians' room for about seven hours daily, five days weekly, usually for three weeks. *In the absence of research interests* [illegible] kept once every three or four days, but

[illegible]

longer. From the doctor's standpoint there is [illegible] while gathering experience, in following the daily changes in the patient's sensitivity to the drug used and in having before him a chart of the blood pressure changes in various postures, together with a note on the relationship between the various symptoms which may occur and the level of the blood pressure at the time.

This is by far the best way of obtaining control, and a technician [illegible] available at every hypertensive centre. Blood pres-

[illegible]

is confined to bed. Blood pressures for routine control are not measured in the lying posture because our patients on ganglion blocking drugs only adopt the lying posture as a temporary measure to combat the effect of an inadvertent overdose

[illegible]

the workings of the drugs, and in our experience the technician is invaluable in educating patients, any special points she cannot answer being dealt with when the doctor comes round or at the outpatient sessions.

The few patients who are now on injection treatment are given instructions about injections and the use of the tuberculin syringe at an early stage, and the

[illegible]

sive symptoms occur or if the systolic blood pressure falls below 110 mm in the sitting posture

Where practicable any trial made with veratrum alkaloids should not be conducted in the same room as methonium trials, as the toxic

effects of the former may upset other patients and may invalidate the results of methonium *trials.*

When ganglion blocking drugs are used each test dose during the initial period is prescribed in terms of the effects recorded with the preceding doses. Thus the doctor in charge is consulted twice or thrice daily, either at the hospital or by telephone. Alternatively minor dose adjustments may be left in the hands of a well-trained technician. As adjustments are made by the addition or subtraction of the standard dose increment (Table XIX 2) for the drug used, the procedure is simple.

When Rauwolfia alkaloids alone are employed it may be satisfactory to dispense with all-day tests if the casual blood pressures at clinic visits provide adequate evidence of a sufficient control over blood pressure levels. In any case only occasional all-day tests will be needed. *Fewer tests* are required when Rauwolfia alkaloids are used in combination with ganglion blocking drugs.

Rich and [illegible] [illegible] Rose. [illegible] with [illegible] [illegible] necessary for the proper control of treatment by ganglion blocking agents.

## (2) The "Standing Test"

[illegible] co[illegible]

Patients who have received approximately the correct dose of hexamethonium or other ganglion blocking agent commonly notice that, although they are comfortable in the sitting posture and substantially comfortable when moving about quietly or when standing still for a few seconds, they become uncomfortable and dizzy or faint when they stand quietly for a full minute in the erect posture. In a hypertensive patient this symptom indicates that there has been a substantial fall of blood pressure. The "standing test" must be carried out at a time when the drug action is at its height. This time will depend on the drug used and the method of administration but is also subject to individual variation. Usually the patient is aware, subjectively, of the time of maximum drug action.

We find in practice that the majority of patients who, at the time of maximum drug action, have difficulty in standing quietly for a full minute are upon a régime which gives a sufficient, or sometimes slightly excessive, fall of the blood pressure. In most instances we are able to assure such patients that the dose is adequate even when casual blood pressures at an outpatient clinic are high. This has been confirmed a great many times by all-day technician tests. If, under normal conditions and without deliberately standing still, they have symptoms such as dizziness or faintness, then the dose will be reduced by whatever

is the standard dosage increment for the drug (see Table XIX 2) to just below the dose producing such symptoms.

The magnitude of each dose given (usually there are two or three daily) can be adjusted by the patient's response to quiet standing.

[illegible]

increment below the dose which causes slight faintness. Until full drug

[illegible]

time.

The test is not strictly an accurate one because the relationship between subjective sensations and blood pressure level is not precise. The "standing test" can be made into a much more valuable guide if early in the course of treatment a patient is given a dose sufficient to produce a mild degree of faintness on standing. The blood pressure fall from this dose (in standing and sitting postures) is recorded by a technician who notes the relationship between the level of the blood pressure and the occurrence of symptoms. For example, it may be found that a patient has symptoms when standing with a systolic pressure of, say, 120 or 110 mm. In such patients the "standing test" may be used with confidence.

Every few months in the early stages of treatment it is desirable to make sure that the relationship between blood pressure level and the occurrence of symptoms has not changed. As patients become habituated to lower blood pressure levels they are able to tolerate such pressures with fewer symptoms. Thus occasionally symptoms may occur at the outset of treatment with a pressure as high as 160 mm.; later symptoms may only occur when the systolic pressure falls to 100 mm.

[illegible]

dose which causes faintness on standing. In such patients a full scale trial over a period of three hours or more will be a very helpful guide to the dosage which should be used.

[illegible]

Under most circumstances this patient would take no harm from such a level, but it is wiser to aim at levels such as 120 to 130 systolic during the trough of the blood pressure fall

### (3) By Symptoms Indicative of Drug Action

At an outpatient clinic an account of symptomatology is a much better guide to the efficiency of treatment with ganglion blocking drugs

TABLE XIX 3. *Effect of Stimulus Situation on the Blood Pressure level in Patients Whose Blood Pressures have been Reduced by the Action of Hexamethonium Bromide*

| Case No | Before Hexamethonium Bromide Injection | After Hexamethonium Bromide Injection | | | | | | Nature of Stimulus Situation |
|---|---|---|---|---|---|---|---|---|
| | Average casual blood pressure | Blood pressure a few minutes before stimulus situation | | Blood pressure during stimulus situation | | Rise of blood pressure | | |
| | | *Sitting* | *Standing* | *Sitting* | *Standing* | *Sitting* | *Standing* | |
| 284 | 222/148 | 188/132 | 166/138 | 210/132 | 190/144 | 22/— | 24/6 | House physician speaks to patient |
| 254 | 212/146 | 190/140 | 159/138 | 202/146 | 186/146 | 12/6 | 27 8 | Had a visitor |
| 295 | 204/142 | 174/102 | 198/112 | 224/122 | 206/112 | 50/20 | 8/— | Had a visitor |
| 291 | 194/128 | 120/92 | — | 192/128 | — | 72/36 | — | Annoyed — would not state reason |
| 294 | 198/142 | — | 174/128 | — | 202/128 | — | 28/— | Doctor speaking to patient while blood pressure was taken |
| 289 | 268/150 | 178/122 | 172/126 | 208/132 | 204/138 | 30/10 | 32/12 | Something fell in corridor outside |
| 289 | 268/150 | 194/126 | 188/132 | 210/138 | 210/136 | 16/12 | 22/4 | Talking to doctor |
| 289 | 268/150 | 182/124 | 174/126 | 234/144 | 212/138 | 52/20 | 38/12 | Visit from doctor |
| 49 | 234/154 | 174/126 | 154/102 | 192/128 | 172/112 | 18/2 | 18/10 | Hospital visiting hour |
| 266 | 225/125 | 152/92 | 132/96 | 200/142 | 158/120 | 48/4 | 26/24 | House physician takes blood sample |
| 159 | 240/155 | 162/142 | 120/92 | 192/142 | 146/100 | 30/— | 26/8 | Student with patient |
| 159 | 240/155 | 148/108 | 114/82 | 192/134 | 152/118 | 44/26 | 38/36 | Hospital visiting hour |
| 159 | 240/155 | 144/102 | — | 202/128 | — | 58/26 | — | Student with patient |
| 273 | 204/132 | 174/90 | 168/98 | 192/102 | 204/118 | 18/8 | 36/20 | Ward round — doctors arrive at next bed to patient |

than is the casual blood pressure taken at the clinic. Making due allowance for personality, it can usually be assumed that if a patient, who has been on e[illegible] for some months, feels it imperative to sit dow[illegible]
injection, then the blood pr[illegible]
near or to below the normal level. Tests on patients can be used to indicate the level of the blood pressure at which dizziness occurs, thereby providing circumstantial evidence of the probable level of the minimum blood pressure level under home conditions. *The duration of* the f[illegible] even in patients who experience hypotensive sym[illegible]
hour [illegible]
cause such as recent emotional stress or overactivity, it can usually be assumed that the régime is defective and that the doses of the ganglion blocking drug need to be increased, the spacing between doses adjusted, or a supplementary dose given in order to prolong the blood pressure fall. The same usually applies when there has been a return of breathlessness, dizziness or other reversible symptoms. Where the dosage is adequate it may be found that some other defect in the régime is responsible for inadequate blood pressure fall as, for example, if the patient rests in the recumbent posture for a good proportion of the day or during the night. If the patient sleeps flat in bed a morning headache is not infrequent, and this is commonly relieved if the patient sleeps propped up at an angle of 45 degrees. It must be borne in mind that control of posture is as important as control of dose in determining adequate falls in the blood pressure level.

Many patients, without being uncomfortable, acquire a subjective awareness of the approximate blood pressure level and can inform the doctor correctly when an adjustment of dose is required.

In a number of patients, when the blood pressure is high, the elongation of the [illegible]

## (4) Casual Blood Pressures

[illegible]

occasions of a patient's visits to outpatient clinics or a doctor's office. The blood pressure is very labile in patients taking methonium drugs so that the blood pressure rises high with activity and emotion (Smirk and Alstad, 1951, Freis, 1954b; Harington and Rosenheim, 1954). I[t] is now common knowledge that patients who show high pressures a[t] clinic visits may experience hypotensive episodes at home; and whe[n]

there are no spontaneous hypotensive symptoms, these may be exhibited when the patient performs the "standing test". We have noted many times that if during a test conducted by technicians a doctor arrives and speaks to the patients or if there is tenseness or emotion from some other cause the blood pressure level will be found to be higher (Table XIX 3).

After several three to six hour tests have shown the response to the drug (oral or injected) to be predictable under test conditions the patient ceases to attend the testing department and attends at the hypertensive outpatient clinic with many other patients. It is found almost invariably that the blood pressure, even measured by the same technician before the patient goes in to the doctor, is some 20, and occasionally 40 or 60 mm. Hg higher than it was when taken in the testing department at a corresponding time after the injection was made or the oral dose was taken. If the effect of the dose is tried out again over a three to six hour period at the testing department the hypotensive activity is confirmed. Table XIX 4 indicates the relationship between three to six hour test blood pressures and clinic blood pressures in a number of patients.

When Rauwolfia alkaloids are used as a background treatment, in combination with ganglion blocking drugs, there is much less fluctuation of the blood pressure level and casual blood pressures, measured at appropriate times, are often a good indication of the degree of blood pressure reduction.

TABLE XIX 4. *Comparison of Blood Pressure Levels at Corresponding Times After an Injection of Hexamethonium Bromide Measured at a Routine Outpatient Clinic and in the Course of Three to six-Hour Tests with the Drug*

| Case No. | Blood Pressures Without Hexamethonium Bromide | | Blood Pressures Taken at Corresponding Times After Injections of Hexamethonium Bromide | |
|---|---|---|---|---|
| | Casual Blood pressure | Basal Blood pressure | *Casual Blood Pressure* Taken at routine visit to outpatient clinic | *Casual Blood Pressure* Taken during a three to six hour test with the drug |
| 251 | 232/154 | 178/118 | 184/122 | 152/108 |
| 252 | 240/140 | 210/144 | 192/132 | 162/126 |
| 255 | 200/120 | 173/120 | 144/82 | 142/108 |
| 295 | 210/120 | 178/108 | 188/114 | 156/114 |
| 272 | 220/140 | 148/96 | 138/98 | 122/94 |
| 294 | 218/130 | 138/90 | 184/132 | 162/108 |
| 283 | 224/168 | 184/120 | 190/112 | 164/118 |

*It appears that once the blood pressure has been reduced to an appreciable* [illegible] *without Rauwolfia), its lability is* [illegible]

[illegible] *to explain why some authors reporting symptomatic* [illegible] *fall of blood pressure has resulted from the administration of methonium salts.*

[illegible] *effects of Rauwolfia alkaloids used in combination* [illegible]

[illegible] *very useful guide to the adequacy of blood pressure control.*

## (5) Home Blood Pressures

Freis (1954b) has made a valuable study of the relationship between [illegible] and pressures taken at the doctor's office in [illegible] these drugs than casual blood pressures at the doctor's office or clinic. This is due to the great lability of the blood pressure in such patients. Schroeder (1954) also instructs his patients or a member of the family in blood pressure measurement Dustan et al. (1955) also evaluate their results in terms of home blood pressures and study the weekly averages. In my own more limited experience home blood pressures are satisfactory for some patients though I retain a preference for control by discussion of symptoms and by the "standing test", aided by three to six hour tests by technicians should doubts arise about the adequacy of a régime.

## (6) Use of Tests with Placebos

Even methonium salts or veratrum alkaloids may appear to be reducing the blood pressure when, in actual fact, the dose being inadequate, they are merely acting as placebos (Fig XIX 5). Even blood pressures taken at 20-minute intervals during three to six hour tests may be deceptive, as may be shown by the effect of administering a placebo under conditions exactly comparable with those under which hypotensive drugs are administered. The placebo, given either by injection or by mouth, is followed in most patients by a fall of blood pressure In many patients the blood pressure will fall without administration of a placebo. The fall of blood pressure continues for perhaps one, one and a half, or even two hours and then begins to rise again. Thus, if the observations start at about 9 a.m. the blood pressure is often rising again towards lunch time. The fall of blood pressure represents the patient's accommodation to the environment of the

clinic, and the later rise seems to be related to a certain degree o "chair weariness" and general restlessness.

The falls of blood pressure following administration of a placebo o

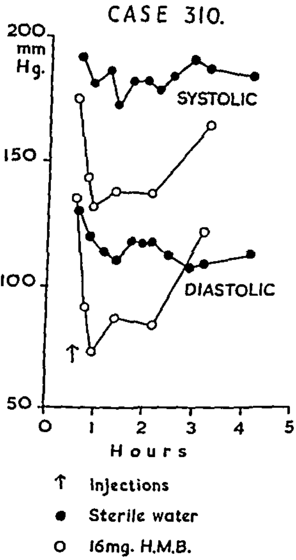



Fig XIX 5

Comparison of the effects of a placebo and hexamethonium (H M.B.). The placebo led to a 20 mm decrease in the diastolic blood pressure

simple habituation to environment may be from 20 to 40 mm. Hg systolic, 5 to 20 mm. Hg diastolic. When known hypotensive drugs are administered, such as methonium salts or veratrum alkaloids, it is commonly assumed that any fall of blood pressure is due to the specific hypotensive action of the substance, and this conclusion seems to derive support if the blood pressure starts to rise again towards the

Hg diastolic are seldom due solely to ...

## PRACTICAL DETAILS

### Method of Initiating Treatment Suitable for Patients Resident in Hospital or Under All-Day Observation at Hospital by a Technician Service

**Intravenous Injections.**—These are required only for emergencies. ... lmonary oedema, cardiac asthma or severe breath- ...

... portant not to give an overdose as such patients cannot ... to combat hypotension Hence, we titrate to find the appropriate dose. The procedure is to have the patient sitting up vertically, preferably with the feet down, in a cardiac bed; alternatively seated in a comfortable chair. In hospital, hexamethonium salts are the most suitable for emergencies as the duration of action of the doses recommended, when given intravenously, is only 1½ hours and the hypotensive action can be maintained afterwards by giving subcutaneous injections.

For intravenous administration in hypertensive patients a suitable dose in a non-tolerant patient is 7.5 mg. (as hexamethonium ion 4.2 mg.) at intervals of 3 minutes until an effect is obtained. For accuracy, a tuberculin-type syringe is essential if the usual 10 per cent solution is used The effect of an intravenous dose, administered with the patient in the sitting posture, is usually evident in 1½ minutes. If the patient has acquired an unknown degree of drug toleration, give 7 5 mg. at intervals of 1 minute

In most instances instructions will be left for the patient to have a subcutaneous injection as the blood pressure rises again, or as symptoms return, or at the end of some stated period, say 2 hours; and thereafter at 3 or 4-hourly intervals, until a proper régime of treatment can be instituted. If hexamethonium is unavailable one of the other ganglion blocking agents, such as pentolinium, can be ...

as the action develops a little less rapidly.

**Subcutaneous Injections.** — The use of subcutaneous *injections* remains necessary for a few patients. In malignant hypertension and hypertensive heart failure there is an advantage in starting treatment by subcutaneous injections. In heart failure this is because the patient is brought under control more rapidly; in malignant hypertension because patients are often much troubled by alimentary side effects

in the early stages of treatment, and usually are more comfortable on injections for the first one or two months of treatment.

For routine subcutaneous treatment hexamethonium is less suitable than pentolinium. Chlorisondamine has not been long available but it seems that its aqueous solution has as long an action as that of injections of pentolinium retard (solution in polyvinyl pyrrolidone) and for injection it may prove to be more satisfactory. Mecamylamine has not been available long. By injection is has no pronounced advantage over chlorisondamine, and parasympathetic side effects may be troublesome.

*Hexamethonium salts.* — For subcutaneous administration the initial dose is 15 mg. of hexamethonium bromide (as hexamethonium ion 8.4 mg.), but feeble elderly patients should have an initial dose of 7.5 mg. An action may be perceptible in 5 minutes, the trough of the blood pressure fall usually occurs within 20 minutes, and the action may last 2 to 3 hours. Large doses, such as 100 or 200 mg., may be required when drug toleration has developed; their absorption is often slower and the action may last more than 3 hours. Subcutaneous injections are usually given thrice daily at intervals of 4 hours or more. Even so, the blood pressure often rises to high levels before the next dose is due. The use of repeated doses of hexamethonium subcutaneously as a method of treatment for hypertension has been superseded by the use of longer acting drugs in the few cases where parenteral administration is still necessary.

The above remarks apply to hexamethonium chloride, except that when the dose is expressed as the salt, 12 mg. of hexamethonium chloride is equivalent to 15 mg. of hexamethonium bromide.

*Hexamethonium bromide dissolved in 25 per cent polyvinyl pyrrolidone.* — Observations were made with 10 per cent and with 20 per cent hexamethonium bromide or M. & B. 1863 dissolved in 25 per cent aqueous solution of polyvinyl pyrrolidone, molecular weight mainly below 60,000 (Smirk, 1952b). To these were added 0.5 per cent chlorbutol as an antiseptic and local anaesthetic, and in some instances 1/2,000 ephedrine hydrochloride was added to delay further the absorption by inducing local vasoconstriction. When the effect of a simple aqueous solution of a methonium salt is compared with an injection of the same amount of the methonium salt dissolved in 25 per cent polyvinyl pyrrolidone the fall in blood pressure is less and often of shorter duration. If, however, the dose of methonium salt in polyvinyl pyrrolidone is increased until the original extent of the fall in blood pressure is restored, then it is found that the fall is of greater duration due to the slower absorption of the methonium salts when incorporated in the colloid. The reason is that if the dose is too small then, because of the slow absorption, the concentration in blood fails to rise above the threshold level for more than a short time; hence, the period of blood

pressure fall may actually be reduced when a slow absorbing preparation is employed, unless there is an adequate increase in the dose of methonium ion. Ordinarily the effective hypotensive action is prolonged to 5 or 8 hours. Patients were instructed not to rub the sites of i[illegible] this may promote more rapid absorption and defeat the

[illegible]

This has not necessitated terminating the injections but such patients are reinstructed in injection methods and advised to choose well separated sites for injection.

With these preparations the blood pressure falls less precipitately and many patients find that they are more comfortable after injections of the more slowly absorbed preparations than after simple aqueous solutions. Two or three injections are given daily at intervals of 6 to 8 hours Shirley Smith et al (1954) and Graham and Maxwell (1954) found the prolongation of the blood pressure fall was useful in some hypertensive patients.

The substance polyvinyl pyrrolidone has been used in large amounts as a plasma substitute in transfusion (Hecht and Weese, 1943) and it seems unlikely that it will give rise to any important or delayed toxicity; we have encountered none. In animal experiments, however, there have been reports of neoplastic developments.

This and other retard preparations depending on the use of a colloid vehicle are difficult to get into a syringe, and the availability of drugs with a longer acting time, even in aqueous solution (chlorisondamine and mecamylamine), will probably make the use of polyvinyl pyrrolidone obsolete.

*Hexamethonium bromide dissolved in 20 per cent solution of Dextran.* — Some observations were made with hexamethonium bromide either in 10 per cent or 20 per cent solution, dissolved in commercial dextran, molecular weight 75,000, as used in a plasma substitute [9, 37, 74]. While

[illegible]

dextrans of lower molecular weight. There seems to be no striking improvement with dextrans with average molecular weights of 20,000 and 45,000.

The capacity of these dextrans to delay the absorption of methonium salts corresponds closely with that of the 25 per cent polyvinyl pyrrolidone, but their use has been discontinued in our clinic because of the local reactions

*Ciba 9295 (Pendiomide).* — Parenteral doses of 17 mg. of Ciba 9295 ordinarily have the same pharmacological effects as 15 mg. of hexa-

in the early stages of treatment, and usually are more comfortable on injections for the first one or two months of treatment.

For routine subcutaneous treatment hexamethonium is less suitable than pentolinium. Chlorisondamine has not been long available but it seems that its aqueous solution has as long an action as that of injections of pentolinium retard (solution in polyvinyl pyrrolidone) and for injection it may prove to be more satisfactory. Mecamylamine has not been available long. By injection is has no pronounced advantage over chlorisondamine, and parasympathetic side effects may be troublesome.

*Hexamethonium salts.* — For subcutaneous administration the initial dose is 15 mg. of hexamethonium bromide (as hexamethonium ion 8.4 mg.), but feeble elderly patients should have an initial dose of 7.5 mg. An action may be perceptible in 5 minutes, the trough of the blood pressure fall usually occurs within 20 minutes, and the action may last 2 to 3 hours. Large doses, such as 100 or 200 mg., may be required when drug toleration has developed; their absorption is often slower and the action may last more than 3 hours. Subcutaneous injections are usually given thrice daily at intervals of 4 hours or more. Even so, the blood pressure often rises to high levels before the next dose is due. The use of repeated doses of hexamethonium subcutaneously as a method of treatment for hypertension has been superseded by the use of longer acting drugs in the few cases where parenteral administration is still necessary.

The above remarks apply to hexamethonium chloride, except that when the dose is expressed as the salt, 12 mg. of hexamethonium chloride is equivalent to 15 mg. of hexamethonium bromide.

*Hexamethonium bromide dissolved in 25 per cent polyvinyl pyrrolidone.* — Observations were made with 10 per cent and with 20 per cent hexamethonium bromide or M. & B. 1863 dissolved in 25 per cent aqueous solution of polyvinyl pyrrolidone, molecular weight mainly below 60,000 (Smirk, 1952b). To these were added 0.5 per cent chlorbutol as an antiseptic and local anaesthetic, and in some instances 1/2,000 ephedrine hydrochloride was added to delay further the absorption by inducing local vasoconstriction. When the effect of a simple aqueous solution of a methonium salt is compared with an injection of the same amount of the methonium salt dissolved in 25 per cent polyvinyl pyrrolidone the fall in blood pressure is less and often of shorter duration. If, however, the dose of methonium salt in polyvinyl pyrrolidone is increased until the original extent of the fall in blood pressure is restored, then it is found that the fall is of greater duration due to the slower absorption of the methonium salts when incorporated in the colloid. The reason is that if the dose is too small then, because of the slow absorption, the concentration in blood fails to rise above the threshold level for more than a short time; hence, the period of blood

better drug for oral use[1,2,4,13,28,36,45,46,49,56,58,63,75,83a,86,90,91,92,93] and for two years comparatively few of our patients have needed parenteral therapy.

Preliminary observations suggest that chlorisondamine, a rather more powerful drug than pentolinium, is therapeutically equivalent to it: certainly chlorisondamine (Ecolid) may be used successfully by mouth. Mecamylamine (Inversine), a secondary amine, has a pharmacological action which, after absorption, seems to be similar to that of methonium compounds, but it is so well absorbed from the alimentary tract that the oral and subcutaneous doses are similar.

The principle used in starting treatment, however, remains the same for all these drugs. For each drug it is necessary to state a suitable *starting dose*, and also the *dose increment* by which the starting dose [illegible] so as to maintain the hypotensive action while

[illegible]

tion. Eventually a stable dose is attained.

*Oral hexamethonium salts.* — Hexamethonium was originally made available as the bromide in 250 mg. tablets, the dose being from a half up to six tablets thrice daily, according to the state of toleration and the sensitivity of the patient[13,48,51,68,80,94,100]. With the larger doses symptoms of bromism occurred[61,97] and the blood bromide concentration rose to levels such as 100 mg. per cent. Hence, other salts are now preferred, such as hexamethonium bitartrate in tablets of 350 mg., the amount of methonium ion in these tablets being approximately that in 250 mg. tablets of hexamethonium bromide. The tablets are best administered dissolved in half a glass of water before a meal. This improves absorption and less of the drug is needed to produce a fall in the blood pressure. Hexamethonium chloride (Methium) is also available in 125 and 250 mg. tablets.

As a few patients are unusually sensitive to ganglion blocking drugs the initial dose should be one-half tablet of either hexamethonium bitartrate or chloride thrice daily, dissolved in water and taken before meals. Each dose may be raised by one-half tablet until either an adequate fall of blood pressure is obtained or until toxic symptoms occur. It is probably unwise to raise the total daily dose beyond 18 tablets, as such doses often lead to gastro-intestinal symptoms. From a single oral dose the blood pressure fall may last 2 to 5 hours, and the interval between doses is determined by the observed activity. Some

[illegible]

an excessive action[48,63]. Hence the irregularity of alimentary absorp-

methonium bromide. Cross-toleration is also exhibited between this substance, hexamethonium bromide and M. & B. 1863, but the exact relationship between the doses noted for hexamethonium bromide and M. & B. 1863 does not obtain for Ciba 9295. It is safe at any stage in the development of drug toleration to change from any given subcutaneous dose of hexamethonium bromide to an equal dose of Ciba 9295, or from any given dose of M. & B. 1863 to twice the dose of Ciba 9295, but the reverse is not true. When drug toleration has developed, it is found in some instances that the equivalent dose of hexamethonium bromide is as little as one-half of the dose of Ciba 9295. So far as effects on the blood pressure are concerned, when adjustments of dosage have been made there seems to be no other important difference between hexamethonium and Ciba 9295. The same side effects are exhibited by Ciba 9295, but we have not sufficient experience to say whether any of them may be avoided in an individual patient by using Ciba 9295 instead of hexamethonium bromide.

Ciba 9295 (Pendiomide) seems, therefore, to be less effective than hexamethonium as a hypotensive drug and like hexamethonium may now be regarded as superseded by more active substances, such as pentolinium, chlorisondamine and mecamylamine.

*Pentolinium bitartrate.* — By subcutaneous injection a suitable initial dose is 3 mg. for the average hypertensive patient and 1.5 mg. for feeble, senile or salt-restricted patients. Toleration develops to a much smaller degree than with hexamethonium and cross-toleration is also less prominent, so that development of a full measure of drug toleration to hexamethonium does not induce a high degree of toleration to pentolinium.

There is a longer period of action than with hexamethonium — often 5 hours with a subcutaneous dose; so that for continued treatment by subcutaneous injections pentolinium is preferable to hexamethonium. Usually three doses daily are required for effective control. As with hexamethonium, the dosage is extremely critical. When a subcutaneous dose has produced little or no fall of blood pressure the amount by which the dose should be increased in the early stages is 1 mg.; later the dose increment may be larger in some cases.

*Pentolinium retard* (pentolinium dissolved in polyvinyl pyrrolidone solution) has been a very useful preparation. The objections to it are those referred to in connection with similar preparations of hexamethonium.

**Oral Therapy.** — When hexamethonium was the ganglion blocking drug used in our clinic we preferred subcutaneous injection [48, 71, 93]. Several British writers who have used hexamethonium bitartrate orally have expressed a similar preference for the subcutaneous route, but oral hexamethonium in the form of the chloride is still widely used in U.S.A. Pentolinium (Ansolysen), however, is usually regarded as a

20 mg. for pentolinium and 10 mg. for chlorisondamine. The increments by which these doses may be increa[illegible] 20 mg. (sometimes 10 mg. in the early stages and 40 mg. later)
for chlorisondamine (Smirk and Ha[illegible]
has developed and the dose is stable, 100 to 1,000 mg. [illegible]
may be required daily.

The maximum effect of an oral dose of pentolinium taken fasting m[illegible] 3 hours after administration. The period of [illegible]

[illegible]

It is possible that the difference in the efficiency [illegible] of hexamethonium chloride and pentolinium bitartrate is not as great as between hexamethonium bitartrate and pentolinium bitartrate.

In most patients and with all three drugs, we find that an increment has to be added to the dose daily in the early stages of treatment and later at intervals of several days or a week. Eventually the dose becomes comparatively stable, sometimes after a month and usually within two months

There are few patients to whom the following rule does not apply (e g anginal cases), but in general the aim with all three compounds is the same, namely, to reduce the systolic blood pressure, in the standing posture, in the trough of the blood pressure fall to 120 mm. Hg or as near to this as can be managed. For brevity we refer to the trough blood pressure (standing) When dosage adjustments are made on the basis of 3 to 6-hour tests by technicians, it becomes possible to

[illegible]

so far, we have been unable to define any clear cut difference between the actions of pentolinium and chlorisondamine, but we have the impression that high dose patients may tolerate chlorisondamine rather better than pentolinium. Some milder cases have had feelings of indefinable malaise with chlorisondamine which were not present with pentolinium The Wellcome drug 139.C.55 may be used in the same way as pentolinium and chlorisondamine, with an initial oral dose in the region of 25 mg and an increment of 25 mg. An occasional patient on oral dosage finds it more satisfactory than other ganglion blocking drugs but in general blood pressures have been less well controlled.

As regards mecamylamine, our experience is more recent. Several

tion [48, 60, 91] leads sometimes to variations in the extent of the blood pressure fall, such that a patient may be comfortable one day and have to lie down because of an excessive blood pressure fall on another day. Some patients have sufficient regularity in the degree of absorption to permit the continued oral use of hexamethonium for blood pressure reduction, even after development of drug toleration. Not infrequently, however, and sometimes after a number of days or weeks of successful therapy, an episode of diarrhoea or diarrhoea and vomiting, or sometimes of excessive constipation, makes a temporary interruption of treatment necessary. Many patients had so much difficulty with these symptoms that they were unable to continue administration of hexamethonium by the oral route and before other drugs became available they had to be treated by thrice daily subcutaneous injections. Turner (1950) in a careful study of the use of oral hexamethonium concluded that it had limited usefulness. Kilpatrick and Smirk (1952) found that only 1 in 4 or 1 in 5 patients were able to maintain effective treatment with oral dosage of hexamethonium bitartrate. Most authors writing from England, Australia and New Zealand, and for the reasons mentioned above, have expressed a preference for parenteral administration if hexamethonium is to be used as a hypotensive agent (Smirk and Alstad, 1951; Kilpatrick and Smirk, 1952; McMichael, 1952; McQueen and Trewin, 1952; Rosenheim, 1952; Shirley Smith et al., 1954; Barnett and Fraser, 1954; Brodziak, 1954; Harington and Rosenheim, 1954; Rytand, 1954). These workers have nearly all used hexamethonium bitartrate. In U.S.A. satisfaction with oral hexamethonium administered usually as the chloride is expressed more frequently (Moyer, Miller and Ford, 1953; Kuhn, 1953; Schroeder, Morrow and Perry, 1953; Ford and Spurr, 1954; Hoobler, 1954, Moser and Mattingly, 1955). In a brief comparison of hexamethonium bitartrate and chloride I gained the impression that when equal doses (of the cation) were administered, the hypotensive action of the chloride was stronger — remarkable if true as the salts should have been ionized. It was of great interest to me to find that Harington (1953), using urinary excretion as an index of alimentary absorption, found that the bitartrate was less well absorbed than the bromide and probably less well absorbed than the chloride.

*Oral pentolinium, chlorisondamine or mecamylamine.* — The procedure for starting treatment with pentolinium is applicable to chlorisondamine and to mecamylamine but allowing for less drug toleration. Pentolinium (Ansolysen) is available in 200, 40 and 10 mg. tablets. Chlorisondamine is available in 50 mg. tablets and mecamylamine in 10 mg. tablets. When the dosage form made available by the manufacturers does not allow of sufficient accuracy in dosage we dissolve the tablets and instruct the patient in the use of a chemical measure.

As set out in Table XIX 2 suitable initial doses for oral therapy are

Such decelerating progression ordinarily maintains doses which reduce the blood pressure despite the development of drug toleration and allows for the fact that drug toleration takes place more rapidly at the [illegible] than later.

[illegible] . The [illegible] raise

all do [illegible]

raisin[illegible]

tion [illegible]

night and in the morning after.

Eventually in two or three months the dose becomes steady (Smirk and Alstad, 1951) and should be stabilized at one dose increment [illegible] produces some dizziness on standing. This dosage [illegible]

[illegible] duce objective improvement in eye grounds and [illegible], even when the measured blood pressure at an outpatient visit seems to be unduly high. It will be found, as explained earlier, that in a careful three to six-hour test, using the dose attained in the above manner, there will be an appreciable fall of blood pressure in most patients. *Where three to six-hour tests are unavailable it is desirable that the blood pressure should be taken at the time of maximum action of the drug used.* [illegible] *one recorded.*

### Instruction of Patients

The period of initiation of treatment lasts two to three months, and during the first three or four weeks the patient should be seen frequently, have 3 to 6-hour control tests where practicable and become familiar with the principles of treatment. For this purpose typewritten instructions for hypertensive patients are most valuable (see Appendix 1), and patients should be encouraged to discuss matters they do not understand. In particular, patients should be told of the ease with which hypotensive symptoms from methonium salts may be relieved by promptly adopting the sitting or, failing immediate relief, the lying posture. The more intelligent patients will learn to arrange minor alterations in their dosage to meet special occasions.

As the instructions are necessarily detailed it is desirable when the patient attends a clinic that a copy should be made available to the patient's private doctor.

### Maintenance of Treatment

Once the patient's dose is comparatively stable the régime becomes

of our patients who had not tolerated pentolinium orally and had had to have injections were able to manage with oral mecamylamine, but one had more trouble with urination than he had noted previously. Other patients of ours have commented on the prominence of parasympathetic side effect. Parasympathetic side effects seem to be less prominent when the appropriate dose of mecamylamine is approached by small increments, say 1 or 2 mg. as required.

### Method of Initiating Treatment Suitable for Private Practice or where there is no Technician Service

Several colleagues have informed me that they have managed effective control tests in patients who visit their rooms and whose blood pressures they measure at intervals between seeing other patients. Others have trained a secretary, nurse or receptionist. The use of the "standing test" as a guide to the extent of the blood pressure fall reduces the number of three to six hour tests required for effective control over blood pressure levels. The procedure for raising the dose in such circumstances, either subcutaneous or oral, is in principle the same as that just outlined but, where control measures are necessarily less detailed, doses are raised by smaller increments or less frequently.

Where 3 to 6-hour control tests are impracticable the following procedure, though less satisfactory, may be tried in the more intelligent and robust patients, but it is probably undesirable in patients with angina, fairly recent cerebral thrombosis, or in patients who are feeble, mentally slow or likely to be left unattended at home. Otherwise the method may be applied with subcutaneous injections or oral therapy.

It is necessary first for the patients to understand the action of the drug used and the means of combating the mildly excessive actions which may occur. We have strong preference for cyclostyled instructions (see Appendix 1). Initial doses for patients who are to begin treatment in their own homes may be halved and the dosage increments reduced similarly (see Table XIX 2)

The doses are raised gradually until a day comes when the patient experiences slight dizziness with the "standing test", or a sensation of general weakness or excessive tiredness on standing and an urgent desire to flop down and rest. When such symptoms are experienced the patient should go back to the previous day's dose. The increases of dose are then resumed, but at intervals of four days instead of daily, until similar symptoms occur. Again the patient retreats to the previous dose which did not cause the symptoms. On resuming dosage increase this takes place by the same amount, but at intervals of one week, until faintness occurs. Then the patient, after regressing to the previous dose, resumes with dosage increases at fortnightly intervals.

nium treatment. In general, patients who present with many symptoms can undertake more work without health impairment than before treatment, but treatment should not become a means of continuing a high pressure existence. Those who present for treatment without symptoms may find that treatment has decreased their energy and drive. Most of our male patients under 60 are gainfully employed and the women are looking after their own homes. Moderate physical effort not attended by symptoms is probably salutary, though stooping and expiratory strains should be avoided.

[illegible] *treatment.* — If a patient [illegible]

be severe. If the drug is omitted for only a few [illegible] of one or two dose increments will be sufficient. If the drug has been omitted for much over a week we usually start with a third or a half of the original dose, but thereafter raise the dose rapidly until symptoms appear. Ultimately the original dose will be restored.

*Need for variations of dosage of methonium salts after the development of drug toleration.* — Most patients after the development of drug toleration exhibit a stable hypotensive response to the appropriate dose of methonium salt except where intercurrent illness alters the sensitivity (see page 654). Sometimes symptoms arise with added [illegible] which can be avoided by a slight increase of dose. [illegible]

have been well controlled for several months sometimes have an unexplained gradual decrease in the dose required. During a febrile illness or post-operatively the dose required to induce the requisite blood pressure may be much reduced. We induced a decrease in drug requirement by T.A.B. injections, evidently the increased sensitivity does not depend on the presence of living organisms. Major surgical operations and injuries such as fractured femur have caused long lasting decrease in dosage requirements (one or two months) with eventual return to the original dose.

Some of our patients who have acted as blood donors have experienced excessive hypotensive responses from their usual doses (see Chapter XVIII). Excessive purgation, episodes of diarrhoea and vomiting and the action of mercurial diuretics all tend to exaggerate the hypotensive effect of ganglionic blocking drugs.

*Transfer from oral to subcutaneous dosage or vice versa.* — Sometimes patients who have been well controlled for a time on oral dosage exhibit side effects such as attacks of lasting constipation or of diarrhoea. If these are infrequent and clear readily on omitting treatment for one or two days *only* then transfer to subcutaneous dosage is unnecessary. Where, however, repeated side effects, or inadequate

easier to control. There are always, however, a number of problems. Some of them may arise also during the stage of initiation of treatment but are not peculiar to that stage.

*Frequency of visits.* — When a patient is well stabilized, visits to the clinic or consulting room are usually at between fortnightly and two-monthly intervals. Side effects and intercurrent maladies may call for dosage adjustments and more frequent visits.

I believe that regular visits are most important. For most patients they should be monthly, even if they are brief.

*Social occasions, journeys, car driving, alcohol.* — Patients commonly ask whether they will be fit for work, a journey or social occasion. By the time a patient feels well enough, the capacity for work and other activities may be judged for the most part on conventional lines. A patient undertaking an unaccustomed journey may do well to have one dose increment less, or even two increments less, than the usual dose so as to avoid any embarrassment from faintness. In anginal cases Whittingham et al. (1949) state that coronary cases should be restricted to 5,000 feet and hypertensives to 8,500 and oxygen should be available. We have found no difficulty so far with air travel in New Zealand where planes travel unpressurized up to 10,000 feet. The standing posture at parties or in the course of travelling in crowded compartments, if it can be anticipated, is an indication for a reduction in dose, usually one or two dose increments, but the patient will learn by experience what this reduction should be. Car driving is to be undertaken at the patient's own risk but, on a stable régime, methonium injections add little to the risk of car driving. Blurring of the vision usually affects near but not distant vision. Patients usually have sufficient warning of hypotensive symptoms to park the car and rest. Symptoms may be noticed, however, on getting out of the car and standing. If the patient is liable to hypotensive symptoms it will be desirable, if only for medicolegal reasons, to avoid intake of alcohol while driving. The effect of moderate alcohol consumption on methonium action is usually unimportant. Large amounts increase the blood pressure falls. Case 21 assured us, on the basis of many trials, that the morning after alcoholic excess a much smaller dose of hexamethonium bromide caused hypotension, and alcoholic headache was relieved consistently. Moyer et al. (1953) state that in hot weather the amount of hexamethonium required is decreased. We have made a corresponding observation with several ganglion blocking drugs. If the patient feels the action of their medicaments has become excessive the dose should be reduced by one or two dose increments.

*Occupations.* — Occupations such as engine-driving, window-cleaning, etc., should not be undertaken but, apart from such risks, the indications as regards occupation and hours of work are very similar to those which would be given to a hypertensive patient not on metho-

## Management of Side Effects due to Blood Pressure Fall or other Circulatory Phenomena

*Hypotensive malaise*
faintness following a fal
while the blood pressure
the patient becomes used
who are habituated to methonium treatment and have got used to lower blood pressures will not exhibit hypotensive symptoms at the same level as they did originally. For example, a patient at first showing hypotensive symptoms at 160 mm. Hg systolic, later only experienced faintness at 110 or 90 mm. Hg systolic. When hypotensive symptoms are developing at any pressure the patient may become quiet, may put down a book or magazine, become a little pale in colour and feel sleepy, even before any sensation of malaise. Frequent, even uncontrollable, yawning may be an early symptom. There may be some dizziness and darkening of vision and soon after a feeling of faintness. When such symptoms appear patients should lie down where they are. If they attempt to get up and move to another room the precipitous fall of blood pressure in the upright posture may cause them to faint, and in some patients with little further warning. Patients who lie down promptly, however, as warning symptoms appear escape without discomfort unless the dose is decidedly excessive. Those who only lie down when compelled to by faintness, or who have collapsed through attempting to walk to a bed, may remain uncomfortable and have an appreciable fall in the blood pressure for as long as an hour and may be not quite well for the rest of the day. If lying down is insufficient then the head may be lowered and the feet raised on to a chair, or the legs doubled up on to the abdomen and the knees squeezed in slightly. If the symptom occurs where it is im-

pressure and may lessen the symptoms to some extent. Those who are troubled intermittently by this symptom may reduce their dose by one or two dose increments before going to a theatre or to church, or visiting friends.

Hypotensive episodes may occur during quiet standing after exercise, or even *during exercise*, due to the occurrence of vasodilatation in the exercised muscles without adequate compensatory response from the sympathetic nervous system. Experiments relating to the effects of hexamethonium on the response to exercise have been described by Hood et al (1953) and Fowler and Guz (1954).

Patients who are unused to methonium hypotension may feel nausea and may even retch a little, but few of them vomit. Later on, nausea seldom accompanies faintness.

control over blood pressure levels, prompt a transfer to subcutaneous injections, it is necessary to begin with a small dose subcutaneously, say 1/30th of the oral dose used — and increased by one or two dose increments per injection until an effect is obtained. In the case of mecamylamine, however, the subcutaneous and oral doses are very similar.

When a patient stabilized on subcutaneous injections is given a trial of oral therapy, an initial dose of five times the subcutaneous dose is safe (mecamylamine and other well absorbed drugs excepted) and the oral dose is then raised to effective levels by two dose increment increases daily.

*Transfer from one ganglion blocking drug to another.* — The development of new ganglion blocking agents which may possess advantages for particular patients raises the question of making a transfer from one compound to another with due regard to the state of drug toleration.

The safest way is to start the new drug at whatever is its standard initial dose (Table XIX 2) and to increase rapidly by two drug increment increases daily, or even at each dose, until the blood pressure begins to fall. Usually small dose adjustments are required for some weeks after making the transfer. An alternative is to administer one dose increment hourly until a fall of blood pressure indicates an approximation to the amount required.

## SIDE EFFECTS FROM GANGLION BLOCKING DRUGS

The side effects of the various ganglion blocking drugs are all very similar, but it should not be assumed that identical side effects will be produced by all such drugs when given in equally hypotensive doses. Indeed, I am fully convinced there are differences which make it possible to make some patients more comfortable by discovering which of several drugs is most suitable. It may be taken for granted, however, that the patients who have severe side effects with one ganglion blocking drug will not avoid them altogether by changing to another.

It has been our experience that side effects usually diminish after several months of treatment. Moyer et al. (1953) and Shirley Smith et al. (1954) also find that side reactions diminish considerably with the passage of time.

The administration of ganglion blocking agents in effective doses to over 500 hypertensive patients provides experience with a diversity of side effects, most of which can be predicted from our knowledge of their pharmacology. But persistence of severe side effects is unusual on a satisfactory régime.

momanometer cuff directly over the site of injection and arranging for periodical inflation and release of the pressure was responsible in our view for saving the life of a patient when a nurse gave an injection of 250 mg. instead of 5 mg. to an unusually methonium-sensitive patient. Alternatively local pressure around the site of injection, by a rubber ring or other convenient means, may be applied prior to complete absorption; i.e. up to 40 minutes after simple aqueous solutions or two hours or more after slow-absorbing solutions.

Overdosage with long acting drugs such as chlorisondamine and mecamylamine may be a little harder to treat than overdosage with hexamethonium.

*Anginal pain.* — In patients who have angina of effort, and occasionally in those who have not had the symptom, undue lowering of the blood pressure may induce anginal pain (Finnerty and Freis, 1950; Smirk and Alstad, 1951), and in such cases great care should be taken to avoid hypotension. Usually it is better not to have systolic pressures lower than 140 mm. in the standing posture. For treatment of pain, the patient should be placed promptly in the horizontal position, which usually results in disappearance of the anginal pain, and the posture should be maintained until the effect of the drug has passed off If recovery is delayed 0.25 to 0.4 ml. of neosynephrine hydrochloride is advised, but not adrenaline. Where patients observe these precautions and have not persisted with doses causing anginal pain we have encountered no lasting ill effects. In one instance we had an example of a clinical and electrocardiographic picture of coronary insufficiency. This was in a patient who, without our knowledge, was persisting with an excessive dose causing coronary pain. Clinical and electrocardiographic recovery took place in the course of a few days

Locket et al. (1951) described a case in which the blood pressure fell to zero in less than 15 minutes after an intramuscular dose of 25 mg of pentamethonium bromide, though the patient was supine. The patient died two hours later and it was felt that a cardiac infarction had occurred Shirley Smith et al. (1954) also encountered a cardiac infarction starting one and a half hours after injection of hexamethonium Koszalka and Walker (1955) reported the case of a patient who developed a myocardial infarct during hypotension [illegible] persisted with sub- [illegible] 100 gr. in one hour. [illegible] m cardiac infarction [illegible] caused by undue lowering of the blood pressure

Our view is that there is no great risk if doses are raised by small increments and if patients do not persist with doses causing pain or excessive blood pressure lowering, and if they lie flat promptly if pain

Hypotension and faintness at the period of maximum drug action occurs with all ganglion blocking drugs if the dose is excessive. With orally administered drugs it is usually related to irregularities in alimentary absorption.

Rauwolfia alkaloids alone seldom cause faintness, even in the exceptional instances in which the blood pressure is restored to normal. When a Rauwolfia alkaloid is used in combination with a ganglion blocking agent, so reducing the requisite dose of the latter, fluctuations of the blood pressure and postural hypotension are reduced, though the average blood pressure level is held nearer to a normal level. Patients on the combination of a Rauwolfia alkaloid and a ganglion blocking agent are less troubled by unexpected faintness when the doses are appropriate.

*Hypotensive shock.* — Measures such as those referred to already should be successful unless an appreciable overdose has been taken or an intercurrent illness has greatly exaggerated the response. In such instances, if the systolic blood pressure in the lying posture is below 80 mm. or if the patient continues to exhibit hypotensive symptoms, 0.25 ml. of 1 per cent neo-synephrine hydrochloride may be injected subcutaneously (Smirk, 1950b) or, in a young person, 0.3 ml. of 1/1000 adrenaline hydrochloride, either of which may be repeated if needed.

Burn (1951) refers to his view that adrenaline should not be used as a means of attempting to counteract methonium hypotension. Our experience using small doses of adrenaline or noradrenaline or neo-synephrine has been entirely satisfactory The doses we use, however, are just enough to restore normotension or a harmless hypotension. Burn advises posterior lobe pituitary extracts. In view of the frequency of coronary disease in hypertensive patients, the diminution in action on repetition of the dose, and the risk attending the subsequent administration of adrenaline, we would advise against the use of posterior pituitary hormone.

If a considerable overdose of a ganglion blocking agent has been taken, a blood transfusion, or a dextran infusion, of 500 to 1000 ml. decreases the hypotensive action and a low pressure circulation may be well maintained in the flat or head down posture, aided if necessary by minimal doses of neosynephrine. Rubber bandages applied to the legs as high up as the thighs have a certain effect in raising the blood pressure (Restall and Smirk, 1952).

Such advanced measures to combat the excessive action of ganglion blocking agents are very rarely needed except in cases of ileus, where absorption from the alimentary canal with decrease of blood volume may lead to excessive and prolonged hypotension (see page 647).

In the event of an inadvertent subcutaneous overdose the method used in our clinic by Fleming (1952) of putting an inflated sphyg-

11, 18, 71, and has not been a cause of discomfort. The symptom has occurred with hexamethonium and pentolinium.

*Ankle oedema not due to congestive heart failure.* — Closely associated [illegible] ndent parts is the appearance [illegible] sitting posture during most of the day and night [illegible] times unilateral, appearing in a limb which has been the site of a [illegible] on a side with more prominent varicose [illegible] is present, oedema may be increased for a while [illegible] usually clears as the congestive heart failure improves.

In this connection it is of interest that Fraser and Lowe (1954) find retention of fluid, as judged by body weight, starts very soon after methonium therapy is instituted but a normal fluid balance is restored later. Probably this is part of the explanation of oedema in dependent parts.

We have observed the oedema while using hexamethonium, pentolinium and combinations of pentolinium and Rauwolfia alkaloids.

*Raynaud's phenomenon in the upper limbs.* — Two patients have reported typical, though mild, attacks of Raynaud's phenomenon in the upper limbs following hexamethonium bromide injections, and other similar cases have been reported to me. Hayden (1954) referred to two cases in his Edward Stirling Lectures, and Shirley Smith et al. (1954) have encountered such cases. After hexamethonium bromide the temperature of the lower limbs in the sitting posture rises, while that of the upper limbs may rise or fall. Sometimes therefore the circulation of the lower limbs is improved at the expense of the upper limbs In two other patients lying in bed Raynaud's attacks involving fingers have been dispersed promptly by a hexamethonium bromide injection. If the manifestation occurs in a patient where continued methonium therapy is desirable the usual precaution of applying local and general warmth will usually make it possible to continue methonium treatment.

*Staggering and unsteadiness following blood pressure fall.* — Apart from hypotension or faintness a sensation of staggerness with objective swaying has followed hexamethonium bromide injections twice in over 400 patients. One patient (Case 13) had methonium treatment for nearly eighteen months without experiencing staggerness as a side effect A minor cerebral thrombosis occurred in the course of treatment from which there was almost complete recovery, but thereafter the patient was unsteady after hexamethonium bromide injections but not after control injections of salt solutions. The staggerness occurred also after M. & B. 1863 but not after injections of pentolinium,

occurs. A number of our hypertensive anginal patients have had considerable increase in capacity to exercise without pain; others have had pain on moderate lowering of the blood pressure and were considered unsuitable for further treatment.

In using pentamethonium, hexamethonium, M. & B. 1863 and pentolinium (Ansolysen) it has seemed to me that the occurrence of angina depended mainly on the extent of the fall of blood pressure. None of the drugs seems to possess an advantage over the others, but more experience is needed with chlorisondamine (Ecolid), 139 C 55 (Presidal) and mecamylamine (Inversine).

*Hypotensive headaches.* — It is not infrequent at the outset of treatment for patients on hexamethonium injections to have a brief headache during the sharp fall of blood pressure. The retard preparation with polyvinyl pyrrolidone usually slows up the absorption sufficiently to prevent this symptom, which is less common with pentolinium and other longer acting drugs.

*Palpitation.* — Some hypertensive patients experience palpitation which commonly decreases or goes with treatment. A few continue to have palpitation while treated, or even develop it for the first time, particularly on standing when the blood pressure falls to a low level. This may be an exaggeration of the normal acceleration of the pulse with a sharp fall of blood pressure [71, 94]. In two patients (Cases 28 and 61) where this complaint caused appreciable discomfort we found that the administration of Hydergine (a mixture of the hydrogenated ergot alkaloids dihydroergocornine, dihydroergocristine, dihydroergokryptine in doses of 0.083 mg. of each per tablet) relieved the palpitation. Surprisingly enough, in one patient the relief was to some extent lasting, in that after a few weeks on Hydergine the patient was able to manage with an occasional dose of this substance. Neither of these patients was neurotic.

The patients who experienced this symptom were receiving hexamethonium but there is no reason to believe that, in this respect, hexamethonium differs from other methonium compounds.

*Reflex hyperpnoea.* — In a few patients the rapid drop of blood pressure is associated with a short period of hyperpnoea, probably of reflex origin. This is seldom distressing and usually passes off with habituation to lower blood pressure levels. We have not studied ways of overcoming this, and we have not encountered patients in whom the symptom was of sufficient moment to deserve treatment other than reassurance. The symptom has occurred after hexamethonium and after pentolinium. The main importance of this side effect is that it should not be confused with impairment of the cardiac reserve.

*Warmth of the feet.* — A number of patients have commented on unusual warmth of the feet, even to discarding shoes or slippers. This is apparently due to increase in the blood flow of dependent parts

paralysis when the blood pressure was reduced considerably and restoration of function after the blood pressure returned to normal.

If methonium treatment is to be continued in such patients the extent of the fall should be modest and distinctly above the level at which the numbness, tingling or weakness occurred. The sensation of numbness and tingling due to the local vasoconstriction of a Raynaud's phenomenon should not be confused with effects due to ischaemia of higher centres.

*Amblyopia.* — Amblyopia lasting as long as 15 minutes was noted in 3 subjects by Fazekas et al. (1955) during acute reduction of the blood pressure. We have also encountered temporary loss of vision, but of short duration.

*Heaviness and drooping of the arms.* — Some patients complain that at the height of action of hexamethonium bromide the arms feel heavy and tasks which involve lifting the arms, such as washing dishes, are difficult. In most instances, with encouragement, the grip as measured by a dynamometer is not significantly below normal. I am quite clear in my mind that this symptom is induced by the drugs, though a psychological overlay is doubtless present as well sometimes.

Wylie and Churchill-Davidson (1951) were impressed by the general muscular weakness after large doses of hexamethonium and thought this was probably an effect similar to that of decamethonium. Shirley Smith et al. (1954) thought the weakness of muscles was probably due to decrease in the blood supply. In regard to this last suggestion, a doctor patient of mine gave me the history that he gets some muscular aching and stiffness, as after severe exercise, when he uses his arms much at a time when the blood pressure is low, but not otherwise This observation would be more easily explained as an effect of decreased blood supply.

*Nitrogen retention.* — Blood pressure reduction does not usually lead to nitrogen retention in patients with moderate degrees of renal insufficiency, but close observation with repetition of blood urea or non-protein nitrogen estimations is essential.

Hayden (1954) considers that the death of two renal cases in his series may have been accelerated by reducing the pressure. It may be difficult to decide on the proper course of action when congestive heart failure and substantial renal insufficiency combine to cause considerable nitrogen retention. Sometimes relief of the heart failure improves excretion.

*Comment on carnification of the lungs.* — Morrison (1953) described 3 patients who developed lung changes which, as it seemed at the time, might have been a complication of long-term hexamethonium therapy. All three had malignant or pre-malignant hypertension, two of them had congestive heart failure, and the third chronic nephritis. An important clinical manifestation was shortness of breath which was

although the doses given were equally effective in blood pressure lowering. Possibly methonium compounds differ in the relationship between cerebral and general vasodilatation.

*Aphasia, paresis and sensory disturbances following administration of methonium salts.* — A number of patients in our clinic have exhibited a temporary, though mild, unilateral loss of power, numbness or tingling following a strong methonium-induced fall of blood pressure; the same has occurred after veratrum alkaloids. This suggests a pre-existing local cerebral ischaemia disclosed by lowering the blood pressure. Within a few weeks of such transitory nervous manifestations, two of our patients and one other case in which we had been consulted developed cerebral thrombosis, in one case fatal. Two of the patients were on and one off methonium treatment at the time. We think the symptom is somewhat unfavourable, indicating the greater likelihood of a cerebral accident whether the methonium treatment be continued or not. Apparently the immediate risk of permanent damage is not great. All patients we have encountered have made a full recovery from the hypotensive episode; but it seems that some of these patients are ready to thrombose and treatment, while revealing this situation, neither retards nor accelerates the event.

A courageous middle-aged spinster, handicapped by angina which occurred on the slightest provocation, had obtained relief by a somewhat elaborate combination of pentolinium, methyl thiouracil and Peritrate. Unfortunately, when she had considerable drops of blood pressure (though not to normal levels) she developed a pronounced hemiplegia from which recoveries were complete though the occurrences were alarming. After about twenty recurrences of and recoveries from the hemiplegia we renewed the question of abandoning methonium therapy. But as her capacity to get about appeared to depend on maintaining a degree of blood pressure reduction she declined to abandon the treatment.

We had another patient with mild pre-senile dementia (well cared for by her relatives) who became aphasic and incapable of activity, though conscious of her surroundings, if the blood pressure fell too low. These manifestations recurred on several occasions always with complete recovery.

Shirley Smith et al. (1954) referred to a patient whose speech became slurred two hours after an injection. They discontinued hexamethonium therapy. In another patient a hemiplegia occurred from which there was complete recovery. Locket et al. (1951) also described hemiplegia occurring in association with methonium treatment. One of our patients developed a fatal cerebral thrombosis in the course of a prolonged episode of hypotension for which we had no explanation.

Hood (1956) has also encountered patients who have had temporary

paralysis when the blood pressure was reduced considerably and restoration of function after the blood pressure returned to normal.

If methonium treatment is to be continued in such patients the extent of the fall should be modest and distinctly above the level at which the numbness, tingling or weakness occurred. The sensation of numbness and tingling due to the local vasoconstriction of a Raynaud's phenomenon should not be confused with effects due to ischaemia of higher centres

*Amblyopia.* — Amblyopia [illegible]
3 subjects by Fazekas et al. [illegible]
pressure. We have also encountered temporary loss of vision, but of short duration.

*Heaviness and drooping of the arms.* — Some patients complain that at the height of action of hexamethonium bromide the arms feel heavy [illegible] involve lifting the arms, such as washing dishes, are [illegible]

[illegible] in my mind that this symptom is induced by the drugs, though a psychological overlay is doubtless present as well sometimes.

Wylie and Churchill-Davidson (1951) were impressed by the general muscular weakness after large doses of hexamethonium and thought this was probably an effect similar to that of decamethonium. Shirley Smith et al. (1954) thought the weakness of muscles was probably due to decrease in the blood supply. In regard to this last suggestion, a doctor patient of mine gave me the history that he gets some muscular aching and stiffness, as after severe exercise, when he uses his arms much at a time when the blood pressure is low, but not otherwise. This observation would be more easily explained as an effect of decreased blood supply.

*Nitrogen retention.* — Blood pressure reduction does not usually lead to nitrogen retention in patients with moderate degrees of renal insufficiency, but close observation with repetition of blood urea or non-protein nitrogen estimations is essential.

Hayden (1954) considers that the death of two renal cases in his [illegible]

able nitrogen retention Sometimes relief of the heart failure improves excretion

*Comment on carnification of the lungs.* — Morrison (1953) described 3 patients who developed lung changes which, as it seemed at the time, might have been a complication of long-term hexamethonium therapy. All three had malignant or pre-malignant hypertension, two of them had congestive heart failure, and the third chronic nephritis. An important clinical manifestation was shortness of breath which was

relieved by lying flat. Chest X-rays showed symmetrical opacities in the upper and mid zones. There was carnification of lung tissue at autopsy and it was considered that there had been organization of intra-alveolar fibrinous exudate (Fig. XIX 6). Further details were given in a paper by Doniach, Morrison and Steiner (1954). They conclude that the phenomenon is one which may be encountered in the absence of hexamethonium in patients dying of heart failure with uraemia (Doniach, 1947). In the cases they refer to there was no attack of acute pulmonary oedema and the condition may represent the effect of a sufficiently long survival to allow the organization of exudate to occur. They do not think that the condition is an indication to discontinue the drug, and in one instance where the drug was discontinued death occurred rapidly. Hamman and Rich (1944) described such a condition at a time when hexamethonium was not in use. Morrow, Schroeder and Perry (1953) had five such cases, and Robillard et al. (1955) also reported a case of pulmonary infiltration which, like some of Morrison's cases had malignant hypertension.

We have not encountered any such case among patients under treatment with ganglion blocking drugs. We have encountered two patients, one in the malignant and the other in the pre-malignant phase, in whom appearances similar to those described by Doniach were found radiologically before starting hexamethonium treatment. The lung changes cannot have been far advanced as they cleared [illegible] blood pressure fall. The absence of this condition as a complication of therapy in over 400 cases suggests that it may have been avoided, as seems logical, by the sitting posture, and by obtaining adequate falls of blood pressure.

*Permanent or long-lasting damage from blood pressure lowering.* — The risks to the hypertensive patient of not lowering the blood pressure adequately far outweigh the risk of any lasting damage from excessive blood pressure reduction. With care in the control of hypotensive therapy the risks of permanent damage are small, but some cause for apprehension is of more frequent occurrence. In patients with coronary disease, coronary insufficiency or cardiac infarction may occur (see page 654) and in patients with cerebral arteriosclerosis cerebral thrombosis has been described (see page 654).

Gillan (1953) quoted his experience with two cases of left-sided blindness following anaesthesia with the Gillies spinal block technique. No hexamethonium was used here and the author thought that the blindness was probably due to pressure on the eye ball in the course of the anaesthetic. The observation is, however, of interest in connection with a similar report by Goldsmith and Hewer (1952) of unilateral loss

of sight with partial recovery after using hexamethonium for controlled hypotension in anaesthesia. In their case they thought that the condition was probably due to spasm of the central retinal artery. A case of permanent blindness after hexamethonium has been described



Fig XIX 6

Periphery of left lower lobe Elastic and Van Gieson, X 205, showing organizing fibrinous plugs within alveoli and alveolar ducts and a prominent interalveolar pore. (Doniach, I, Morrison, B, and Steiner, R E, Brit Heart J, 16 101, 1954)

by Bruce (1955). The blood pressure recorded shortly before the occurrence was 180/110.

## Management of Side Effects not due to Blood Pressure Fall

Most of the side effects which are not due to the blood pressure fall are due to blockade of parasympathetic ganglia (Fig. XIX 7)

*Blurring of the vision.* — Blurring of the vision occurs to a variable degree with all ganglion blocking drugs, some patients being unable to read, others barely detecting a difference in the near point for close vision. *The symptom is due to blocking of the sympathetic and parasympathetic ganglia.* There is often some slight dilatation of the pupils and in a bright light there is more consciousness of the glare. A few patients have used dark glasses. There has been no permanent change in vision and if the drug is omitted the blurring goes. As drug toleration develops with continued administration, blurring of the vision, though seldom disappearing, often becomes less prominent.

Among the ganglion blocking drugs we have used in our clinic; pentamethonium, hexamethonium, M. & B. 1863, M. & B. 1950, pentolinium, chlorisondamine, 139 C 55 and mecamylamine, the substance M. & B. 1950 causes relatively less blurring of vision. There are also [illegible]

[illegible]

without losing the hypotensive action.

*The addition to the régime of a small dose of a Rauwolfia* alkaloid increases the effect of ganglion blocking drugs on the sympathetic vasomotor system without affecting parasympathetic functions Thus, *smaller doses of ganglion blocking drugs suffice and parasympathetic* side effects are diminished Alternatively, blurring may be corrected at the time of its occurrence by the use of positive lenses up to 2, or *occasionally 3, diopters* We keep in our clinic a range of positive lenses arranged to clip on the frame of spectacles normally worn by the patient. In this way patients discover during their clinic attendances what correction is required during the drug action for such activities as reading or sewing. A personal set can then be ordered from the optician.

Eye drops of 1/32nd. or 1/16th per cent of physostigmine have been helpful, higher concentrations cause headaches. Harington and Rosenheim (1954) have also used spectacles to correct for loss of accommodation and Murphy (1951) has used physostigmine drops.

*Sore eyes.* — A mild feeling of soreness about the eyes has been encountered. Dilatation of conjunctival vessels is not an uncommon effect of ganglion blocking drugs and occurs sometimes with Rauwolfia alkaloids; but the sensation of soreness is probably related also to drying of the conjunctivae following decreased parasympathetic activity The symptom has often disappeared spontaneously

*Dryness of the mouth.* — Mouth dryness is another parasympathetic

effect common to all ganglion blocking drugs and present to some degree in most patients. Exceptionally it causes discomfort in eating and appetite loss. Mild loss of appetite has been a help to some overweight patients. The symptom is often relieved by parasympathetic

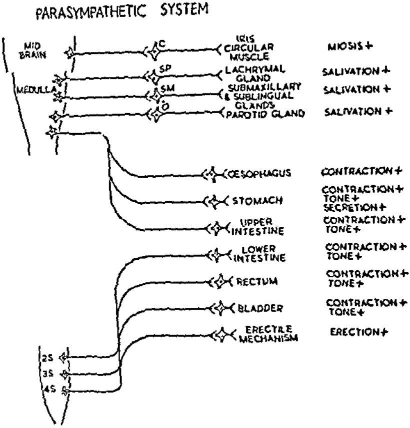



Fig XIX 7
Physiological effects of stimulation of the parasympathetic system.

stimulants administered before meals (Freis, 1954a; Mills and Moyer,

alkaloid often relieves dryness of the mouth and loss of appetite.

*Glossitis and sore mouth.* — Fortunately this symptom is not usually persistent, but its presence causes much discomfort in eating. Usually it clears spontaneously using mouth washes, even without modification

tion) of an injection of 100 μg. of vitamin B12 has been associated with disappearance of this symptom in all cases except one, where there was also some angular stomatitis. In this case the condition cleared up on the addition of large doses of riboflavine, a measure which Murphy (1951) found valuable in such cases.

*Bad taste in the mouth.* — This has been referred to spontaneously by a few patients — perhaps 3 per cent. It has occurred with pentolinium as well as hexamethonium. It has been associated sometimes with dry mouth and with glossitis for which treatment may be applied. Peppermint mouth washes or chewing gum are useful. My impression is that the symptom usually clears spontaneously.

*Dryness of the skin.* — This has not been a cause of discomfort in our patients, but some remark upon it. It occurs with all ganglion blocking agents. Patients previously troubled by excessive sweating have lost this symptom. [illegible] of the sweat gl[illegible] face creams on account of skin dryness is not uncommon in female patients.

*Constipation.* — Constipation is a common complaint of patients on [illegible] than hexamethonium; chlorisondamine and mecamylamine can both cause severe constipation. This side effect is particularly troublesome in patients who have had the complaint even in the absence of ganglion blocking drugs. The constipation may be followed by bouts of diarrhoea; if uncorrected it may lead to paralytic ileus, especially with oral administration of the drugs. This is nearly always prevented by well diluted magnesium sulphate taken before breakfast or, alternatively, by liquid paraffin or liquid paraffin with agar and small doses of phenolphthalein (P.A.P. emulsion). The most favoured remedy in our clinic is the P.A.P. emulsion.

There is no objection to patients taking their favourite purgative in doses sufficient to produce a motion. Variation in the intensity of methonium therapy with constipation or with diarrhoea has been noted by a number of patients and it is desirable as far as possible to maintain an even bowel action, more particularly in patients who are on oral therapy. A small dose of purgative regularly, just sufficient to allow of a daily motion, is preferable to drastic measures after a period of constipation. The administration of magnesium sulphate or other osmotic purgatives in concentrated solution and large doses has caused faintness occasionally — presumably from diminished blood volume.

A 15 mg. tablet or even 1½ tablets of neostigmine taken with water 20 minutes before breakfast may help to secure a bowel action. Finnerty and Freis (1951) recommended urethane β-methylcholine chloride

(urocholine) 5 to 15 mg. by mouth twice or three times daily to control any tendency to constipation and ileus.

McQueen and Trewin (1952) used carbachol in doses of 0.5 to 1.0 mg. as tablets, weekly or twice weekly, to supplement the effect of the liquid paraffin.

The use of combined therapy — a Rauwolfia alkaloid with a ganglion blocking agent — is associated with less constipation than the use of a ganglion blocking agent alone.

*Actual abdominal distension, feelings of fullness or flatulence.* — These may occur with all ganglion blocking agents, especially early in treatment or if dosage increases are made rapidly, whether by injection or orally. The symptom is comparatively slight when drug toleration has developed. In several patients the symptom has caused a degree of distress. Where there has been colicky pain atropine has given relief. In some cases parasympathetic stimulants have been used, for example, oral doses of 2 mg. pilocarpine, 0.25 mg. carbachol or 15 mg. of neostigmine.

*Paralytic ileus.* — In 1951 a number of authors [7, 82, 84, 99] described [illegible] [illegible] [illegible] [illegible] damine and Freis and Wilson (1955) observed ileus with mecam[illegible] as well as with hexamethonium. Ileus is likely to occur when patients in the initial stages of treatment are placed flat in bed and doses of ganglion blocking drugs are administered until such time as an adequate fall of blood pressure is obtained in the horizontal posture. This is bad technique Good falls of blood pressure can be obtained with smaller doses if the patient is propped up in bed with a back rest at an angle of 45 degrees. Under these circumstances the risk of paralytic ileus is much reduced. Even so, in our own series of cases, a severe ileus has occurred in approximately 1 or 2 per cent of patients and mild ileus is more frequent The fully developed condition involves a serious risk to life. complete constipation and absence of bowel sounds and abdominal distension being associated with vomiting of material with a faecal odour. The blood pressure in these patients is usually low, partly due to a state of shock, and also from absorption of the ganglion blocking agent retained in the alimentary canal. When paralytic ileus develops, or is threatened, it is necessary to interrupt temporarily the administration of ganglion blocking substances. Ordinarily prostigmine will be administered in doses of 0 5 mg. or more, subcutaneously If the state of shock is not quickly relieved, a transfusion of 1 to 2 pints of blood, or an intravenous injection of a litre of dextran solution, or even of normal saline, may be of assistance. If the blood pressure remains dangerously low, the administration, as required, of 0.25 ml. of 1 per cent neosynephrine will usually maintain a satis-

factory circulation. An enema may assist the emptying of the bowels, and emptying of the stomach contents by continued gastric suction may help.

Where paralytic ileus has developed in a patient who has been on oral therapy it will usually be practicable to resume therapy if the ganglion blocking agent is combined with reserpine, so diminishing the dose employed. If, however, the paralytic ileus has developed in a patient who already had the advantage of reserpine it is better to transfer from oral therapy to treatment by subcutaneous injections, morning and night. The risk of paralytic ileus seems to be appreciably less when methonium compounds are injected, as compared with when they are administered by mouth. Theoretically, ileus from oral mecamylamine should be less dangerous than from other drugs available at present, because as it is well absorbed there should be no alimentary residues, and no continued absorption of the drug from the obstructed intestines after administration is discontinued.

*Diarrhoea.* — This may occur in the course of methonium therapy by injection but it is, I think, more frequent in patients on oral therapy. Aside from the use of purgatives, the diarrhoea may arise in three ways. It may occur from disturbance of autonomic regulation. Some patients regularly have an increase in bowel action on at least some ganglion blocking agents. Diarrhoea from this cause is more frequent with pentolinium than with hexamethonium. Presumably in some patients the sympathetic innervation of the bowels is more effectively blockaded than the parasympathetic. When diarrhoea is due to the predominance of sympathetic blockade, the occurrence of the lo[illegible]

drug. [illegible]

of autonomic innervation, the diarrhoea only occurred when a given subcutaneous dose was surpassed. The diarrhoea developed regularly on the same day and cleared by the next day if the dose was reduced again.

In other instances we thought the diarrhoea was the result of achlorhydria and an infection. For example, if a number of patients in a ward are affected by epidemic diarrhoea there tends to be an unduly high proportion of patients on ganglion blocking drugs among them. Exceptionally we have been able to help by administering an acid mixture, but usually such mixtures have not been beneficial and have caused indigestion.

The third cause of diarrhoea is the result of bowel upset due to several days of constipation.

Mild diarrhoea can be controlled by the use of a chalk, or chalk and opium mixture, but stronger episodes are best treated by omitting a few doses of the drug. Diarrhoea with oral therapy has sometimes made it necessary to change to subcutaneous injections which usually can be taken without important alimentary side effects.

*Urinary retention or delay in bladder emptying.* — Slowness in emptying the urinary bladder has been noticed by a number of patients, chiefly male, but ordinarily the symptom is not troublesome. When present it is most prominent early in treatment and ameliorates with continued administration, presumably because more toleration is acquired for parasympathetic than for sympathetic effects. In a few instances where continuous subcutaneous injection was employed (Smirk, 1951b) there was complete inability to empty the bladder, which passed off if injections were stopped for a few hours. Palmer (1952) noted an increase in bladder emptying time. A few of our patients have had more difficulty in emptying the bladder after transfer to the long-acting mecamylamine. Perhaps such cases would be better with a shorter acting drug such as pentolinium which leaves an interval between doses for bladder emptying.

*Nocturnal polyuria.* — This is not uncommon after hexamethonium bromide. With increase in the circulation through dependent parts oedema, visible or invisible, may accumulate during the day and be reabsorbed and excreted at night. The symptom, when it has developed after using ganglion blocking drugs, has not had any untoward asso- [illegible] has been compatible with excellent [illegible] ities.

[illegible] — While young male patients have noted a decrease in sexual desire and prolongation of intercourse, this has not usually been of important degree. After 45 loss of libido and potentia were not infr [illegible] sexual activity was res [illegible] nium compounds. Vera[illegible] but in most patients adequate control over blood pressure levels is not obtained without toxic effects. Reduction of the dose of ganglion blocking agent by use of the combination with a Rauwolfia alkaloid, and timing the event to correspond with minimal drug action, and occasionally the use of a tablet of neostigmine 20 minutes beforehand, have helped most patients. According to some of my patients pentolinium has less effect on the sexual function than hexamethonium. The substitution of two doses of protoveratrine for two consecutive doses of the ganglion blocking agent will be satisfactory in some patients who do not get relief by other measures. If protoveratrine is not used regularly, effective action of the drug is more likely to be preserved.

*Shivering and sensations of cold.* — Attacks of shivering are not infrequent in the course of treatment with ganglion blocking drugs and many patients feel the cold more than the average person. An occasional patient feels cool in warm weather. Usually warmer clothing is sufficient to overcome this symptom, which in time lessens spontaneously. In one or two patients there has been a difference between

one methonium compound and another in this respect — for example in Case 262 shivering was much more prominent with pentolinium than with hexamethonium bromide for the same degree of blood pressure reduction. We have observed a well developed rigor without abnormal rise of temperature on two or three occasions. The body temperature is usually slightly decreased in patients taking ganglion blocking drugs. It is possible that this side effect may prove to be mainly a circulatory phenomenon.

*Reactions at the sites of injection.* — A local bruise may occur in any patient, usually due to the site chosen, but a few patients have had several local haemorrhages. In one elderly patient quite extensive painless bruising occurred at the site of each injection. Local irritation with lump formation is sometimes reported after injections of retard preparations. These are almost always due to patients injecting into the deeper layers of the skin instead of subcutaneously. After instruction in injection methods the difficulty has been overcome in most instances.

*Nasal blockage.* — A sensation and objective evidence that the nose is 'stuffed up' has been clearly related in some patients to the use of ganglion blocking drugs. This symptom has not persisted. The degree of nasal obstruction may be quite minor but in a few instances has been pronounced. When Rauwolfia alkaloids are used alone or in combination with ganglion blocking drugs the symptom occurs much more frequently. Sometimes this symptom disappears spontaneously. Usually relief can be obtained by the use of a Tuamine inhaler.

## Comment on Side Effects

The dosage of ganglion blocking drugs should be such that a fully adequate fall of blood pressure is obtained, though not necessarily in the first week or two of treatment. It must be accepted that some side effects will occur.

Hypotensive episodes are not, properly speaking, side effects; they are an indication that the dose is too large or the total daily dose has not been properly distributed so that excessive action at one time is associated with inadequate action at another.

Adjustments of any dosage scheme made with the object of lessening side effects should not be allowed to interfere with the main object, which is blood pressure reduction. Side effects can nearly always be relieved without interfering with the efficiency of the régime, but it may take months in some patients to find a way round their particular difficulty. The most consistent way of relieving side effects is by combining the ganglion blocking drug with a Rauwolfia alkaloid. This may sometimes raise new problems (Chapter XVII) but, in general, patients are much more comfortable on the combination.

In our experience parasym[illegible] side effects often decrease spontaneously but, in any case, [illegible]
other measures, it is nearly [illegible]
and often comfortable.

## TREATMENT OF CERTAIN MANIFESTATIONS AND COMPLICATIONS OF HYPERTENSION, WITH SPECIAL REFERENCE TO THE RELATIONSHIP BETWEEN HYPOTENSIVE AND OTHER THERAPY

### Cardiac Asthma

Adequate control over blood pressure levels is commonly sufficient to prevent the recurrence of attacks of cardiac asthma without the use of other therapy, such as mercurial diuretics, digitalis, or salt-free diet (Smirk and Alstad, 1951). Glajchen (1951) also referred to the very prompt relief of attacks of left ventricular failure following the intravenous administration of hexamethonium bromide or, on occasion, of subcutaneous administration. The acute attack of cardiac asthma is best treated by an appropriate injection of a methonium salt with the patient in the sitting posture If the patient is already on methonium treatment the accustomed dose may be administered if a sufficient time has elapsed since the preceding dose The relief of cardiac asthma is sometimes dramatic: from severe respiratory distress to comparative comfort in 2 or 3 minutes

Administration of a ganglion blocking drug will be regulated by the blood pressure level prior to each injection After a substantial fall in [illegible]

[illegible] should be given, then intravenous administration of the appropriate dose in fractional amounts over a period of 10 minutes will bring the quickest relief by the safest means The appropriate dose is the one which lowers the blood pressure to the desired extent and, expressed as hexamethonium bromide, varies in different patients from as little as 7 5 mg. to as much as 100 mg. Excessive dosage must be avoided as the horizontal posture cannot be used to counteract hypotension in orthopnoeic patients

The discomfort of the patient in an acute attack of asthma may be lessened as usual by 1/6th or 1/4th of a grain of morphine; 1/200 grain of atropine may be useful as it lessens the tendency towards vomiting from morphine, but larger doses are better avoided.

We have preferred, as far as is possible, to treat patients with cardiac asthma by methonium therapy without the aid of digitalis,

one methonium compound and another in this respect — for example in Case 262 shivering was much more prominent with pentolinium than with hexamethonium bromide for the same degree of blood pressure reduction. We have observed a well developed rigor without abnormal rise of temperature on two or three occasions. The body temperature is usually slightly decreased in patients taking ganglion blocking drugs. It is possible that this side effect may prove to be mainly a circulatory phenomenon.

*Reactions at the sites of injection.* — A local bruise may occur in any patient, usually due to the site chosen, but a few patients have had several local haemorrhages. In one elderly patient quite extensive painless bruising occurred at the site of each injection. Local irritation with lump formation is sometimes reported after injections of retard preparations. These are almost always due to patients injecting into the deeper layers of the skin instead of subcutaneously. After instruction in injection methods the difficulty has been overcome in most instances.

*Nasal blockage.* — A sensation and objective evidence that the nose is 'stuffed up' has been clearly related in some patients to the use of ganglion blocking drugs. This symptom has not persisted. The degree of nasal obstruction may be quite minor but in a few instances has been pronounced. When Rauwolfia alkaloids are used alone or in combination with ganglion blocking drugs the symptom occurs much more frequently. Sometimes this symptom disappears spontaneously. Usually relief can be obtained by the use of a Tuamine inhaler.

## Comment on Side Effects

The dosage of ganglion blocking drugs should be such that a fully adequate fall of blood pressure is obtained, though not necessarily in the first week or two of treatment. It must be accepted that some side effects will occur.

Hypotensive episodes are not, properly speaking, side effects; they are an indication that the dose is too large or the total daily dose has not been properly distributed so that excessive action at one time is associated with inadequate action at another.

Adjustments of any dosage scheme made with the object of lessening side effects should not be allowed to interfere with the main object, which is blood pressure reduction. Side effects can nearly always be relieved without interfering with the efficiency of the régime, but it may take months in some patients to find a way round their particular difficulty. The most consistent way of relieving side effects is by combining the ganglion blocking drug with a Rauwolfia alkaloid. This may sometimes raise new problems (Chapter XVII) but, in general, patients are much more comfortable on the combination.

In our experience parasympathetic side effects often decrease spontaneously but, in any case, with the aid of Rauwolfia alkaloids and other measures, it is nearly always possible to make a régime tolerable and often comfortable.

## TREATMENT OF CERTAIN MANIFESTATIONS AND COMPLICATIONS OF HYPERTENSION, WITH SPECIAL REFERENCE TO THE RELATIONSHIP BETWEEN HYPOTENSIVE AND OTHER THERAPY

### Cardiac Asthma

Adequate control over blood pressure levels is commonly sufficient to prevent the recurrence of attacks of cardiac asthma without the use of other therapy, such as mercurial diuretics, digitalis, or salt-free diet (Smirk and Alstad, 1951). Glajchen (1951) also referred to the very prompt relief of attacks of left ventricular failure following the intravenous administration of hexamethonium bromide or, on occasion, of subcutaneous administration. The acute attack of cardiac asthma is [illegible] treatment the accustomed dose may be administered if a sufficient time has elapsed since the preceding dose The relief of cardiac asthma is sometimes dramatic· from severe respiratory distress to comparative comfort in 2 or 3 minutes

[illegible] should be given, then intravenous administration of the appropriate dose in fractional amounts over a period of 10 minutes will bring the quickest relief by the safest means The appropriate dose is the one which lowers the blood pressure to the desired extent and, expressed as hexamethonium bromide, varies in different patients from as little as 7.5 mg. to as much as 100 mg. Excessive dosage must be avoided as the horizontal posture cannot be used to counteract hypotension in orthopnoeic patients.

The discomfort of the patient in an acute attack of asthma may be lessened as usual by 1/6th or 1/4th of a grain of morphine, 1/200 grain of atropine may be useful as it lessens the tendency towards vomiting from morphine, but larger doses are better avoided

We have preferred, as far as is possible, to treat patients with cardiac asthma by methonium therapy without the aid of digitalis,

mersalyl or salt-free diet. By doing so we have a guide to the efficiency of the methonium treatment and the patient, observing the close relationship between freedom from attacks and effective reduction of blood pressure, co-operates willingly. Ultimately, if cardiac breakdown occurs, additional measures are available which have not yet been exploited. In elderly and deteriorated patients who are not responding to methonium salts only, the first additional measure to use is a mercurial diuretic (mersalyl 2 ml. intramuscularly) because, if the deterioration is temporary, omission of the mercurial diuretic for a few days gives information as to whether blood pressure reduction alone will prove adequate. The second measure to adopt is salt restriction, and lastly digitalis. In patients who, when first seen, are already on a digitalis-mersalyl régime, we maintain this unchanged to appraise more exactly the effect of blood pressure reduction. In most instances we have been able to omit the digitalis and mersalyl at a later date; in others it has been necessary to maintain one or other form of ancillary treatment.

In some elderly or deteriorated patients, where nocturnal attacks of cardiac asthma have not been prevented, it has been found that a more substantial additional oral dose of the ganglion blocking drug at bedtime may prevent nocturnal attacks. If the attack tends to occur in the early morning the drug should be taken with a glass of milk and a few biscuits to delay absorption. One of our patients who had aortic regurgitation as well as hypertension found out for himself that he could abort his attacks of cardiac asthma by having an additional subcutaneous injection of hexamethonium.

### Congestive Heart Failure in Hypertensives

Initially, in the more acute cases, hexamethonium bromide may be given by fractional intravenous or subcutaneous injection, starting with 5 mg. until sufficient has been given to drop the blood pressure. An important part of the treatment is the use of a cardiac bed with the body inclined at 50 degrees from the horizontal and the legs depressed some 25 degrees from the horizontal. If these measures do not give an important degree of relief within one or two hours mersalyl, and possibly digitalis, are administered, using intravenous Digoxin, 0.25 to 0.5 mg.

In moderate hypertensive heart failure it is better to avoid digitalis and mersalyl and anything more than mild salt restriction (no added salt to the food) for at any rate a period of six days. With good blood pressure reduction using a subcutaneous preparation, improvement occurs within this time in about 50 per cent of patients, more particularly in those who are not in the older age groups. Oral therapy is inapplicable in such cases because of frequent trouble with side effects. To accelerate progress, if that be needed, it is wiser to use

mersalyl, and aminophylline tablets (0.3 g.) first. The reasons for trying to avoid digitalis are those set out in the previous subsection.

It is not to be expected that cardiac asthma and heart failure will be held off indefinitely in hypertensive patients, but there is clear evidence that deterioration is postponed for several years (Chapter XXI). It is of interest that relief of congestive heart failure occurs even with hexamethonium, although the blood pressure may rise to high levels between the injections. This was remarked on by McQueen and Trewin (1952).

Shirley Smith et al. (1954) have administered a night injection only in some patients where cardiac failure seemed to be imminent. Improvements occurred in such patients, indicating that it was not necessary to have control of the blood pressure level over the whole day in order to improve the symptoms.

The experience in our clinic has also been that relief of congestive heart failure may be obtained with intermittent reduction of the blood [illegible] heart failure cases a more drastic control is [illegible]

against the risk of a cerebral accident demands the best control that can be obtained.

## Cardiac Infarction and Coronary Insufficiency

In these conditions the blood pressure usually falls spontaneously. If the blood pressure rises again, methonium treatment may be used to relieve hypertensive manifestations, but the extent of the blood pressure fall should be moderate, and in the trough of the fall should [illegible]

as early as the fifth week.

In angina there is no difficulty in using any of the measures ordinarily employed in conjunction with a methonium régime. Care must be taken if nitrites are used that the patient is in the sitting posture and can lie down if necessary

## Cerebral Haemorrhage, Subarachnoid Haemorrhage, Cerebral Thrombosis

Apart from difficulties which sometimes attend the differentiation of these conditions in states of urgency, it is uncertain whether methonium salts are helpful or otherwise. The topic needs further study. Slightly encouraging results have been obtained in cases of subarachnoid haemorrhage in hypertensive individuals.

In some patients with haemorrhage into the brain substance a state

of resistance to huge doses of hexamethonium developed. It seems very likely in such cases that the release of a humoral agent has led to decrease in the neurogenically maintained fraction of the blood pressure (see Chapter XI).

In a few patients with advancing paralysis, thought to be due to cerebral thrombosis, we decreased the blood pressure by intravenous hexamethonium and noted a further extension of the paralysis which receded when the blood pressure was raised again.

## MANAGEMENT OF INTERCURRENT DISORDERS OCCURRING IN PATIENTS ON HYPOTENSIVE THERAPY

One of the questions I am asked most frequently is whether the treatment of an intercurrent disorder has to be modified when a patient is being treated by a ganglion blocking drug or other hypotensive agent, and whether adjustment of the hypotensive therapy is required.

In general, as the following examples show, there is seldom any modification needed in the procedures for treating intercurrent maladies, but often it is necessary to adjust the treatment of the hypertension.

*Infections.* — Intercurrent infections often, but not invariably, lead to appreciable reduction in the dose of methonium salts needed to produce a substantial fall of blood pressure. If the dose is not reduced the fall in blood pressure may be such that the patient cannot stand or even sit without feeling faint. Febrile colds usually produce only a moderate increase in drug sensitivity but considerable increases have been observed during pneumonia and glandular fever, such that half the usual dose suffices The enhanced sensitivity persists after the febrile state has ended, but usually normal drug tolerance is regained in two or three weeks. If a patient who has been on a stable dose gets excessive falls of blood pressure during an infection the dose should be cut to two-thirds or even to one half, and then raised again by one or two dose increments a time until a satisfactory action is obtained. In some instances the pressure remains down for days or weeks with comparatively little or even with no therapy. There is no danger in leaving a patient off ganglion blocking drugs at a time when his blood pressure is down, but constant vigilance is needed and the pressure should not be allowed to rise high again for a febrile illness with rise of blood pressure may precipitate congestive heart failure or cardiac asthma. Treatment of the infection by antibiotics and sulphonamides need not be modified. Fluid balance should be maintained as dehydration exaggerates the action of ganglion blocking agents. The bowels

should be kept regular without, if possible, the use of large doses of purgatives.

*Alimentary Disorders.* — The use of methonium salts for the treatment of *peptic ulcer* has been described by Scott, Kay, O'Hare and Simpson (1950). We have had the opportunity of treating a few patients with both hypertensive and peptic ulcer symptoms at the same time and have not been impressed with the usefulness of ganglion blocking drugs for the ulcer symptoms. There is, however, no difficulty in using concurrently any of the drugs ordinarily employed in peptic ulcer patients. It has been stated that the use of Rauwolfia alkaloids should be avoided in peptic ulcer as they may lead to increased acid secretion. We have not, so far, encountered difficulty in such cases when ganglion blocking agents are used also. In a variety of patients with a history of dyspepsia, methonium salts have aggravated or caused a recrudescence of dyspepsia, though not necessarily of the same type. The main symptoms have been loss of appetite, flatulence, sensations of abdominal distension, sometimes visible distension, occasionally vomiting and sometimes colicky pain which responds to atropine.

A patient (Case 70) was referred to us with hypertension and repeated *haematemesis* unassociated with ulcer history and presumably due to gastric erosions. Effective treatment of the high blood pressure was associated with cessation of the episodes of haemetemesis, which have not recurred during four years treatment, first with injections of hexamethonium and later with oral pentolinium. If a patient bleeds while on a ganglion blocking drug the fall of blood pressure resulting from such moderate losses as 250 ml. may be considerable. My impression is that bleeding might be curtailed but we have had no opportunity to make observations. Patients who have had *constipation* tend to have some increase of this following administration of methonium salts, but to a degree which can usually be controlled by the regular use of purgatives Patients susceptible to diarrhoea previous to treatment have not necessarily shown any worsening of the con-

and injections of hexamethonium in 4 cases of ulcerative colitis without hypertension with, at most times, a decrease in the number of bowel actions The measure is, however, purely palliative and the order of relief similar to that obtained by other measures. A patient with

treatment. Stubinger and Koch (1952) obtained improvement in ulcerative colitis with Pendiomide

One patient (Case 50) in the course of treatment for hypertension was discovered to have a *carcinoma of the large bowel* which was removed by radical resection. After this the administration of methonium salts by subcutaneous injection led to frequent attacks of diarrhoea and it seemed reasonable to abandon treatment.

A hypertensive patient who had *diverticulitis*, blood intermittently in the motions and diarrhoea got an important degree of relief from pentolinium. The number of bowel motions was reduced and perhaps relief of intestinal spasm helped.

Grimson (1955) mentions a patient with *fissure in ano* who had to have a rectal operation, the condition having been aggravated by constipation induced by hexamethonium. *Haemorrhoids* also may give more trouble if constipation is pronounced.

*Exacerbation of gall-bladder dyspepsias.* — Murphy (1951) referred to a patient who had had a symptomless cholelithiasis but, on treatment developed vomiting sufficiently severe to require abandonment of oral therapy. We have not had a case as pronounced as this and it has not always been clear in our patients whether gall bladder activity had been influenced by ganglionic blockade or whether recrudescence of symptoms was coincidental. Several of our patients have had a cholecystectomy, and no special problems arose during or after surgical treatment. The combination with Rauwolfia alkaloids may not help gall bladder cases as these alkaloids alone may predispose to gall bladder colic.

*Respiratory disorders.* — Apart from the presence of infection, respiratory disorders have had little influence on methonium therapy. Two hypertensive patients had bronchiectasis, three had chronic bronchitis or emphysema. Bronchial asthma present in two patients under treatment for arterial hypertension apparently did not influence methonium therapy. We have administered methonium salts without benefit or harm to patients with bronchial asthma but without hypertension at a stage when attacks were frequent. A renewal of asthmatic attacks coincided in 1 patient with the use of Rauwolfia alkaloids.

Pneumonia has caused the death of some of our patients, in one instance by pulmonary oedema. My impression is that such patients should be nursed in the sitting posture.

We have not encountered difficulty with any of the drugs ordinarily employed in treating respiratory disorders.

*Circulatory disorders.* — Reference has been made already to the treatment of congestive heart failure, cardiac asthma and patients with coronary diseases.

A number of hypertensive patients have had *cardiac arrhythmias* such as multiple premature systoles, bundle branch block, etc, but no influence on these has been noted with any of the ganglion blocking drugs or Rauwolfia alkaloids

We had hoped that after reduction of the blood pressure there would

treatment of toxic goitre. So far hypotensive therapy ... change to normal rhythm in such cases.

It might be thought that the sympatholytic effect of hexamethonium or other ganglion blocking agents would be of value in promoting an anastomotic circulation in patients with *arteriosclerosis of limb vessels*. Windesheim et al. (1955) find that hexamethonium does not usually ... our experience in several ... but I have not found these drugs causing ... circulation in hypertensive patients who required treatment for their hypertension. There is no objection to the concurrent use of hydergine.

*Central nervous system disorders.* — Reference has been made already to the treatment of cerebral vascular accidents.

A number of patients with cerebral deterioration such as *arteriosclerosis* and *mild senile dementia* have been treated. The main problem in the management of such patients has been the difficulty of securing co-operation, but when intelligent relatives have controlled the régime results have been good.

Patients who in the past have exhibited psychotic illnesses requiring mental hospital treatment have been a source of worry in the clinic. On occasion they have developed peculiar ideas about the effects of treatment which upset other patients in contact with them. When a decision for or against treatment of hypertension is in doubt a history of psychotic epis... risk of recurrenc... should not be ov... with renal hypertension have occurred. No improvement was observed during methonium therapy in one, and in the other convulsive episodes did not recur.

A patient with *epileptic attacks* and hypertension and no definable neurological cause lost the epileptiform attacks entirely following methonium therapy. Another epileptic is unchanged as regards fits. A number of patients have had "encephalopathic" attacks involving paresis, sensory disturbances or unconsciousness prior to treatment which have not recurred or have recurred only at infrequent intervals.

*Endocrine disorders* — There is no difficulty in controlling the blood pressure level in *Cushing's syndrome* by hypotensive drugs. If surgical treatment is to be considered it should be mainly for relief of other features of the disorder. One patient had a thyroidectomy for toxic goitre without any difficulty arising. Antithyroid drugs can be taken by patients on ganglion blocking drugs. I have no experience with the use of cortisone or DOCA in hypertensive patients.

*Rheumatic diseases.* — With some misgivings in each case our clinic arranged to treat a few patients who were much disabled by osteoarthritis and one with ankylosing spondylitis. In each case there was a hypertensive manifestation from which the patient hoped for relief. The results were better than I expected. An important point with patients whose stability is impaired and who may not be able to sit or lie down promptly is to avoid hypotension. The trough of the blood pressure fall (standing) should be in the region of 150 or 140 systolic. In a female patient with bilateral osteoarthritis of the hips movement was slow and breathlessness was a handicap. A vitallium cup operation had been discussed but it was doubtful if she was fit for the surgical procedure. On hypotensive therapy her breathlessness improved, the operation was performed unilaterally and her capacity to get about is much improved. Another patient, a man with hypertensive heart failure and ankylosing spondylitis finds relief from breathlessness a considerable help. Butazolidine has relieved most of his pains. Butazolidine is said by Goodman and Gilman (1955) to be contraindicated in hypertension. It causes electrolyte retention. We did not observe any unusual toxic reactions in patients who had been given butazolidine by their home doctors, but the substance is toxic and its administration requires close supervision.

The administration of cortisone and related endocrine substances would need close supervision as regards the blood pressure level, and some adjustments in the dosage of ganglion blocking drugs would be required.

*Obesity.* — Ganglion blocking drugs sometimes aid the reduction of obesity by causing dryness of the mouth with diminution of appetite. If, however, reserpine is used the appetite is increased and a rise of body weight is usual. Rescinnamine, another Rauwolfia alkaloid, does not increase the appetite to the same degree and sometimes causes a degree of anorexia. Canescine seems to take an intermediate position.

*Skin disorders.* — Skin conditions have not been influenced appreciably by methonium treatment. The skin tends, however, to become dry. Keele (1952) mentions improvement which has occurred in certain cases of hyperhidrosis.

Varicose ulcers are not infrequent as an incidental disability. Several patients under treatment for high blood pressure who had had frequent recurrence of varicose ulcers, found that the ulcers ceased to appear after methonium treatment was established, possibly from improved circulation to the legs. My colleague, Dr. Stringer, has found methonium compounds helpful in the treatment of varicose ulcers.

*Renal disorders.* — Reference has been made already to the problems involved in treating patients with renal insufficiency. Where the renal excretion is impaired the action of ganglion blocking drugs may be prolonged. Hypertensive manifestations are relieved as in essential

stopped or the blood pressure allowed [illegible]

The surgical treatment of unilater[illegible]
persons should not be undertaken in [illegible]
which it rarely does. Such cases respond to hypo[illegible]
the decision to undertake surgical treatment need not take account of the blood pressure level.

*Urinary disorders.* — One patient with frequency of micturition and hypertension was able to retain urine for longer periods than previously. Patients with prostatic hypertrophy usually find that methonium treatment adds to th[illegible] [difficulty] in emptying the bladder. Such patients usually make a [illegible]
injection is taken, or, [illegible]
action is minimal. In most instances urination has been satisfactory after prostatectomy. Patients who have had a hemiplegia may have trouble in emptying the bladder exaggerated by ganglion blocking drugs and may need catheterization or carbachol injections.

*Pregnancy.* — There has been no difficulty in reducing the blood pressure with ganglion blocking drugs either in essential hypertension complicated by pregnancy, in pregnancy toxaemia, or in post-toxaemic hypertension. The method of using ganglion blocking drugs does not differ from that used in essential hypertension. Pregnancy toxaemia is, however, something more than a hypertension in pregnancy and all other measures which have been found helpful should be used additionally, in particular strict curtailment of the salt intake, which will also enhance the action of ganglion blocking drugs.

There may be important effects on the alimentary canal of the foetus. Young (1952) showed in the pregnant rabbit that hexamethonium passes freely across the placental barrier. In the newborn infants of toxaemic mothers treated with hexamethonium Turner (1951) and Mulcahy (1952) observed no harmful effects. We have not noted any harmful effects on the newborn child when hexamethonium or other ganglion blocking agents were stopped on the day before parturition, but foetal deaths have occurred in our experience and we are unable to say whether hexamethonium played any part in these. There seems to be little doubt that sometimes hexamethonium causes paralytic ileus in the unborn child. Morris (1953) referring to the use of hexamethonium bromide in 10 toxaemic mothers reported that 2 babies died with paralytic ileus. Hallum and Hatchuel (1954) describe a case of paralytic ileus which followed the treatment of the mother with 50 mg. of hexamethonium bromide four times daily for eighteen days, up to and including the day of delivery of the child. When full use is made of postural hypotension smaller doses of ganglion blocking

drugs are effective and the risk of toxicity to the child must be appreciably less. None of the series seem to be sufficiently extensive to indicate how often this complication occurs, but stopping the administration of ganglion blocking drugs a few days before parturition should reduce the incidence of the complication.

*Ophthalmic disorders.* — Hypertensive patients with cataract are usually sent to us a short time before surgery is undertaken and a near normal level of the blood pressure is maintained during and for several weeks after operation. The aim is to diminish the risk of intraocular haemorrhage.

Glaucoma might be influenced for the worse by pupillary dilatation but we have not had to treat such a case. Barnett (1952), however, finds the intraocular tension is lessened during hexamethonium hypotension.

*Surgical operations and accidents in the course of treatment with ganglion blocking drugs.* — Patients after operative treatment commonly have a fall of blood pressure which may persist for one or several weeks. This is not related to infection and occurs with "clean" surgical procedures such as an operation for insertion of a vitallium cup. It has occurred after cholecystectomy.

Two of our patients have sustained a fractured thigh (not due to hypotension from drug action). The blood pressure in each case remained down for some weeks after the injury. The blood pressure control must be very lenient during convalescence. Despite precautions one of these patients fell as the result of a hypotensive episode and fractured her wrist.

Our practice is to omit ganglion blocking drugs some five to ten hours before an operation and to resume with appropriate doses (see page 633) as the pressure begins to rise again. It should not be overlooked that improvement in the fitness for operation may be obtained in certain hypertensive patients by two or three months blood pressure reduction.

*Anaesthesia in Hypertensive patients.* — See appendix 3.

## References


1 Agrest, A., and Hoobler, S. W. Long-term management of hypertension with pentolinium tartrate (Ansolysen) J. Amer. med. Ass., 157: 999, 1955.

2 Allen, E. V., Barker, N. W., Hines, E. A., Jr., Kvale, W. F., Shick, R. M., Gifford, R. W., Jr., and Estes, J. E., Jr. Medical treatment of essential hypertension. Proc. Mayo Clin., 29: 459, 1954

3 Arnold, P., and Rosenheim, M. L. Effect of pentamethonium iodide on normal and hypertensive persons. Lancet, 2. 321, 1949

4 Ashby, D. W., O'Neill, J., and Maclean, M. C. Initial control of hypertension with pentolinium tartrate Lancet, 1: 224, 1955

5 BARNETT, A. J. Ocular effects of methonium compounds. Brit. J. Ophthal., 36 393, 1952.
6 BARNETT, A. J., and FRASER, J. R. E. Methonium treatment of arterial hypertensive disease. Alfred Hosp clin Repts, 4: 35, 1954.
7 BOURNE, G., and HOSFORD, J. Methonium compounds in hypertension. Lancet, 1: 527, 1951.
8 BRODZIAK, I. A Hypertension. Bull. post-Grad. Comm. Med Univ. Sydney, 9. 283, 1954.
8a BRUCE, G M Permanent bilateral blindness following the use of hexamethonium chloride. Trans. Amer Ophthal Soc., 53: 107, 1955.
9 BULL, J P., RICKETTS, C, SQUIRE, J. R, MAYCOCK, W. D'A, SPOONER, S J L, MOLLISON, P. L., and PATERSON, J. C. S. Dextran as a plasma substitute. Lancet, 1: 134, 1949
10 BURN, J H. Methonium compounds in hypertension. Lancet, 1: 642, 1951.
11 BURT, C C, and GRAHAM, A J P Pentamethonium and hexamethonium iodide in investigation of peripheral vascular disease and hyperten-

Kong Chin. med Ass, 6 23, 1954
14 DONIACH, I Uremic edema of the lungs. Amer J Roentgenol, 58 620 1947
15 DONIACH, I, MORRISON, B, and STEINER, R E Lung changes during hexamethonium therapy for hypertension Brit. Heart J., 16: 101, 1954
16 DUSTAN, H P, CORCORAN, A. C, SCHNECKLOTH, R., and PAGE, I. H Combination therapy of severe hypertension with ganglion blockers and reserpine Circulation (N Y), 12 698, 1955
17 FAZEKAS, J F, KLEH, J, and PARRISH, A E Cerebral complications of hypotension Ann. intern Med., 43: 165, 1955
18 FINNERTY, F A, Jr, and FREIS, E D Experimental and clinical evaluation in man of hexamethonium (C6), a new ganglion blocking agent. Circulation (N Y), 2: 828, 1950
19 FINNERTY, F. A, Jr, and FREIS, E D Clinical appraisal of hexamethonium (C6) in peripheral vascular diseases New Engl. J. Med, 245: 325, 1951
20 FLEMING, H A Treatment of an overdose of hexamethonium bromide. Lancet, 1 1310, 1952
21 FORD, R. V, and SPURR, C L The treatment of the ambulatory hypertensive patient with hexamethonium administered orally. Amer. Practit. (Philad), 5 251, 1954
21a FOWLER, P B S, and GUZ, A Blood pressure during exercise and the effect of hexamethonium Brit Heart J, 16: 1, 1954
22 FRASER, J R E, and LOWE, T E Fluid retention during methonium therapy Aust. Ann Med, 3 234, 1954
23 FREIS, E D Methonium compounds in hypertension Lancet, 1: 909, 1951.
24 FREIS, E D Recent developments in the treatment of hypertension Med.
25

Importance of home recordings in adjusting dosages Med. Ann. Distr Columbia, 23 363, 1954b

26

27

28 (
vascular hypotension. Canad. med. Ass. J., 69: 294, 1953.

29 GLAJCHEN, D. Hexamethonium in acute ventricular failure. Brit. med. J., 2: 797, 1951.

30 GOLDSMITH, A. J. B., and HEWER, A. J. H. Unilateral amaurosis with partial recovery after using hexamethonium iodide. Brit. med. J., 2: 759, 1952.

31 GOLDSMITH, H. J. Death from hexamethonium ileus. Brit. med. J., 1: 622, 1955.

32 GOODMAN, L. S., and GILMAN, A. The pharmacological basis of therapeutics. The Macmillan Company, New York, 1955.

33 GRAHAM, J. G., and MAXWELL, R. D. H. The medical treatment of hypertension. Brit. med. J., 2: 1250, 1954

34 GREEN, D. M., and ELLIS, E. J. Intravenous hexamethonium sensitivity and responses to oral treatment. Circulation (N Y.), 9: 521, 1954.

35 GRIMSON, K. S. Drugs recently introduced for hypertension. J. Amer. med. Ass., 158: 359, 1955.

36 GROB, D. Management of the patient with primary "essential" hypertension. J. Chronic Dis., 1: 540, 1955.

37 GRÖNWALL, A., and INGLEMAN, B Dextran as a substitute for plasma. Nature (Lond.), 155: 45, 1945.

38 GUNN, J. A., and COOKE, A. M Pilocarpine as an antagonist to the undesired effects of ganglion-blocking agents in the treatment of hypertension. Brit. med. J., 1: 1473, 1954.

39 HALLUM, J. L., and HATCHUEL, W L. F Congenital paralytic ileus in a premature baby as a complication of hexamethonium bromide therapy for toxaemia of pregnancy. Arch. Dis. Childh, 29: 354, 1954.

40 HAMMAN, L., and RICH, A. R. Acute diffuse interstitial fibrosis of the lungs. Bull Johns Hopk. Hosp, 74: 177, 1944

41 HARINGTON, M The absorption and excretion of hexamethonium salts. Clin. Sci, 12: 185, 1953.

42 HARINGTON, M., and ROSENHEIM, M. L Hexamethonium in the treatment of hypertension Lancet, 1: 7, 1954.

43 HAYDEN, J. G. Treatment of hypertension Med. J. Aust, 1: 693, 1954.

44 HECHT, G., and flussigkeitsersatz. Münch med

45 HOOBLER, S W Bull. Amer. Soc. Hosp Pharm., 11: 23, 1954a

46 HOOBLER, S W Treatment of hypertension Amer. J. Med, 17: 259, 1954b.

46a HOOD, B. The problem of blood pressure reduction in cases with advanced vascular damage Personal communication, 1956.

46b HOOD, B., BJÖRK, S, ANGERVALL, G., and RUDBÄCK, H. Muscular exercise ... t of hexamethonium chloride ... 953

47 KEELE, C A. ..., with special reference to paralysis of autonomic ganglia Arch. Middx Hosp., 2: 23, 1952

48 KILPATRICK, J. A, and SMIRK, F. H Comparison of oral and subcutaneous administration of methonium salts in the treatment of high blood pressure. Lancet, 1: 8, 1952.

49 KIRKENDALL, W. M, and CULBERTSON, J. W. Management of systemic arterial hypertension. Arch. intern. Med, 95: 601, 1955.
49a KOSZALKA, M. F., and WALKER, H. C. A hazard of hypertensive drug therapy. J.-Lancet, 75: 368, 1955.
50 KUHN, P. H. The use of oral hexamethonium chloride (Methium) in the treatment of hypertension. Angiology, 4: 105, 1953.
51 LOCKET, S, SWANN, P. G, and GRIEVE, W. S M. Methonium compounds in the treatment of hypertension. Brit. med. J., 1: 778, 1951.
52 LYONS, W. G, and LORD, P. J. Paralytic ileus after hexamethonium. Brit. med. J., 2: 176, 1951
53 MACKEY, W. A Hexamethonium in hypertension. Brit. med. J., 1: 948, 1951
54 MACKEY, W A, and SHAW, G. B. Paralytic ileus after hexamethonium. Brit. med. J., 1· 1205, 1951
55 MCMICHAEL, J. The management of hypertension. Brit. med. J., 1: 933, 1952
56 MCMICHAEL, J., and MURPHY, E. A. Methonium treatment of severe and malignant hypertension. J Chronic Dis., 1· 527, 1955.
57 MCQUEEN, E. G, and TREWIN, E Treatment of hypertension with hexamethonium bromide Med. J. Aust., 2: 425, 1952.
58 MAXWELL, R. D H, and CAMPBELL, A J M New sympathicolytic agents. Lancet, 1 455, 1953
59 MILLS, L. C, and MOYER, J H. Treatment of hypertension with orally and parenterally administered purified extracts of veratrum viride. Arch. intern Med, 90· 587, 1952
60 MILNE, G E., and OLEESKY, S Excretion of the methonium compounds. Lancet, 1 889, 1951
61 MORRIS, N Hexamethonium compounds in the treatment of pre-eclampsia and essential hypertension during pregnancy Lancet, 1: 322 1953.
62 MORRISON, B Parental hexamethonium in hypertension. Brit. med. J. 1. 1291, 1953
63 MORRISON, B, and PATON, W D M Effects of hexamethonium on normal individuals in relation to its concentration in the plasma. Brit. med. J. 1 1299, 1953
64 MORROW, J D, SCHROEDER, H A, and PERRY, H. M Studies on the control of hypertension by hyphex II Toxic reactions and side effects Circulation (N Y), 8 829, 1953
65 MOSER, M, and MATTINGLY, T W I Critical evaluation of drug therapy of hypertension Postgrad Med, 17: 351, 1955
66 MOYER, J H, MILLER, S I, and FORD, R V Orally administered hexamethonium chloride in hypertension J Amer med. Ass, 152. 1121, 1953
67 MULCAHY, R Treatment of toxaemia of pregnancy with hexamethonium bitartrate J Irish med Ass, 31 205, 1952.
68 MURPHY, E A Treatment of hypertension with hexamethonium bromide. Lancet, 2 899, 1951
69 PALMER, A J The management of hypertension with hexamethonium bromide Med J Aust, 2· 428, 1952
70 PLATT, R Hypertensive retinopathy and its medical treatment Quart. J Med, n.s 23· 441, 1954
71 RESTALL, P. A., and SMIRK, F H The treatment of high blood pressure with hexamethonium iodide N Z med. J., 49: 206, 1950.
72 RESTALL, P. A, and SMIRK, F H Regulation of blood pressure levels by hexamethonium bromide and mechanical devices Brit. Heart J, 14 1, 1952.

73 RICH, C. B., and HOLUBITSKY, W. H. The treatment of hypertension with oral hexamethonium. Canad. med. Ass. J., 68: 342, 1953.

74 RICKETTS, C., LORENZ, L., and MAYCOCK, W. D'A. Molecular composition of dextran solutions for intravenous use. Nature (Lond.), 165: 770, 1950.

75 RIVEN, S. S. The use of drugs in the management of hypertension. J. Tenn. med. Ass., 48: 243, 1955.

76 ROBILLARD, R., RIOPELLE, J. L., ADAMKIEWICZ, L., TREMBLAY, G., and GENEST, J. Pulmonary complications during treatment with hexamethonium. Canad. med. Ass. J., 72: 448, 1955.

77 ROSENHEIM, M. L. Discussion on the medical treatment of hypertension. Proc. roy. Soc. Med., 45: 269, 1952.

78 ROSENHEIM, M. L. The treatment of severe hypertension. Brit. med. J., 2: 1181, 1954.

79 RYTAND, D. A. Use of hexamethonium in arterial hypertension. Calif. Med., 80: 375, 1954.

80 SAVILLE, S. Pentamethonium in hypertension. Lancet, 2: 358, 1950.

81 SCHROEDER, H. A. Management of arterial hypertension. Amer. J. Med., 17: 540, 1954.

82 SCHROEDER, H. A., MORROW, J. D., and PERRY, H. M., Jr. Studies on the control of hypertension by hyphex. 1. Effects on blood pressure. Circulation (N.Y.), 8: 672, 1953.

83 SCOTT, L. D. W., [illegible] methonium [illegible]

83a SHELDON, M. B. [illegible] Amer. Practit. (Philadl.), 7. 33, 1956.

84 SMIRK, F. H. Methonium compounds in hypertension. Lancet, 2: 477, 1950a.

85 SMIRK, F. H. Practical details of the methonium treatment of high blood pressure. N. Z. med. J., 49: 637, 1950b.

86 SMIRK, F. H. Methonium halides in high blood pressure. Science, 114: 4, 1951a.

87 SMIRK, F. H. Blood pressure reduction to a selected level by continuous injection of methonium halides (C5 and C6) and the use of an electrically operated syringe. Amer. Heart J., 42: 530, 1951b.

88 SMIRK, F. H. Effects of hexamethonium bromide homologues in man. Proc. Univ. Otago med. Sch., 30: 13, 1952a.

89 SMIRK, F. H. Prolongation of action of hypotensive drugs: Use of polyvinylpyrrolidone and dextrans to lengthen effects of hexamethonium and hexamethylene bis-ethyl-dimethylammonium. Lancet, 2: 695, 1952b.

90 SMIRK, F. H. Action of a new methonium compound in arterial hypertension: Pentamethylene 1.5-bis-N-(N-methyl-pyrrolidinium) bitartrate (M. & B. 2050). Lancet, 1: 457, 1953a.

91 SMIRK, F. H. Practical details of the treatment of hypertension by hexamethonium salts and by pentamethylene 1.5-bis-N-(N-methylpyrrolidinium) bitartrate (M. & B. 2050). N. Z. med. J., 52: 325, 1953b.

92 SMIRK, F. H. Blood pressure reduction in arterial hypertension by hexamethonium and pentapyrrolidinium salts. Amer. J. Med., 17: 839, 1954.

93 SMIRK, F. H. Antihypertensive drugs. Ann. Rev. Med., 6: 279, 1955.

94 SMIRK, F. H., and ALSTAD, K. S. Treatment of arterial hypertension by penta- and hexamethonium salts. Brit. med. J., 1: 1217, 1951.

95 SMIRK, F. H, and HAMILTON, M. Action of "Ecolid" in man. Brit. med. J., 1: 319, 1956.

96 SMITH, K. S, FOWLER, P. B. S, and EDMUNDS, V. Hypertension and its control by hexamethonium Brit. med. J., 2: 1243, 1954.

97 SOMMERVILLE, J, and ALLAN, J. A case of drug eruption induced by hexamethonium bromide. Brit. med. J, 1: 864, 1951.

98 STÜBINGER, H G, and KOCH, B Erfahrungen mit einem ganglien blockierenden Präparat (Pendiomid) in der inneren Medizin. Dtsch. med. Wschr., 77: 1061, 1952.

99 THOMAS, O M, and WILLIAMS, R G. Paralytic ileus after hexamethonium. Brit. med. J, 1: 1331, 1951.

100 TURNER, R. "Medical sympathectomy" in hypertension — A clinical study of methonium compounds Lancet, 2 353, 1950.

101 TURNER, R. Methonium compounds in hypertension Lancet, 1: 408, 1951.

102 WHITTINGHAM, H, BARBOUR, A B, and MACGOWAN, J C Medical fitness for air travel. Brit. med. J., 1 603, 1949.

103 WINDESHEIM, J H, ROTH, G M, and GIFFORD, R. W. The use of hexamethonium in treatment of arteriosclerosis obliterans. Circulation (N.Y). 11 604, 1953

104 WYLIE, W D, and CHURCHILL-DAVIDSON, H C A side-action of hexa- [illegible], 1951

105 [illegible] nium bromide in the [illegible] J Physiol (Lond.), 116 4p, 1952

CHAPTER XX

# COMBINED THERAPY

There has been a growing appreciation of the fact that improvement in the degree of control over blood pressure levels with fewer side effects, can be achieved by combining certain forms of therapy.

Before the present era of drug therapy, it had been noted that patients who had had a sympathectomy would, thereafter, respond better to thiocyanates or to salt restriction. Restall and I noted in 1950 that the effect of hexamethonium was increased by the use of a Kempner rice diet, and enhanced sensitivity to the drug was found in patients who had had a sympathectomy (Smirk and Alstad, 1951). Freis (1951) reported that hydralazine could be used with advantage in combination with hexamethonium, and Schroeder (1951) using oral hexamethonium and oral hydralazine developed a technique of treatment which, in his hands, gave an improved control over the blood pressure level. Wilkins (1952) used Rauwolfia alkaloids in conjunction with either veratrum, hydralazine or occasionally hexamethonium, and since then almost all the combinations of two or more of the following have been tried: hexamethonium, pentolinium, hydralazine, veratrum alkaloids, dibenzyline, Rauwolfia alkaloids and salt restriction. Two recent additions are Rauwolfia alkaloids with chlorisondamine (Ecolid) and with mecamylamine (Inversine).

The usefulness of a combination may be judged by (1) the degree of improvement in the control over the blood pressure level, with particular reference to smoothing the response and lessening the disadvantages of postural hypotension; (2) decrease in the incidence of side effects and of remote toxicity.

The effects of combining certain forms of therapy are definite. Well-established actions are:

1. The increase in the sensitivity to ganglion blocking agents following sympathectomy.
2. The increase in the sensitivity to ganglion blocking agents following severe salt restriction.
3. Increase in the sensitivity to ganglion blocking agents after a period of treatment with Rauwolfia alkaloids (mixed alkaloidal preparations, reserpine, rescinnamine and canescine).

4. Additive effects when hydralazine is combined with a ganglion blocking agent. There is still much dispute, however, about whether the addition of hydralazine to a régime is worthwhile, as there are equally effective forms of therapy involving fewer side effects and no known danger of remote toxicity.

Some physicians start patients on Rauwolfia alkaloids and if the hypotensive action is insufficient add either veratrum alkaloids or hydralazine. If these combinations are insufficiently effective they use the combination of Rauwolfia and a ganglion blocking agent. In our clinic we no longer use veratrum alkaloids and very seldom use hydralazine.

## COMBINATION OF RAUWOLFIA ALKALOIDS WITH A GANGLION BLOCKING AGENT

[illegible] been wide[illegible] Rauwolfia [illegible] 1954, 1955; Smirk, Doyle and McQueen, 1954; Freis, 1954; Singh, 1955; Moser, 1955; Bain, Ashton and Jones, 1955; Talso, 1955; Riven, 1955; Patton, 1955; and Bartorelli, 1956).

The administration of Rauwolfia alkaloids in combination with hexamethonium leads to larger falls of blood pressure than are obtained by hexamethonium alone [6, 8, 10, 18, 20, 30, 46]. An additive effect is also obtained regularly when a Rauwolfia alkaloid is combined with pentolinium [1, 2, 5, 6, 18, 46, 50] or with chlorisondamine [28, 31]. We found the action of 139 C 55 is also increased when combined with Rauwolfia alkaloids. It is of great interest that mecamylamine, a secondary amine with a ganglion blocking action similar to pentolinium, also has its effects enhanced by reserpine [12, 47].

The effects of pentolinium are increased, not only by the use of reserpine and of mixed Rauwolfia alkaloids, but also by the administration of rescinnamine and of canescine (Smirk and McQueen, 1955a, b).

It is clear to me that Rauwolfia alkaloids potentiate the action of [illegible] not merely additive. The [illegible] reserpine, rescinnamine or [illegible] may have no appreciable effect on the blood pressure level, but in substantially all cases, irrespective of whether the Rauwolfia alkaloid has exhibited any effect on the blood pressure, the action of pentolinium is considerably increased by the previous administration of these alkaloids, so that the

fall of blood pressure may be maintained by as little as a third or a half of the original dose of pentolinium.

A further action, which does not seem to be the result of potentiation is that, in patients receiving reserpine, the control over the blood pressure level is much smoother[3, 6, 15, 50], and the tendency of the blood pressure to rise at clinic visits is much less than it is in patients

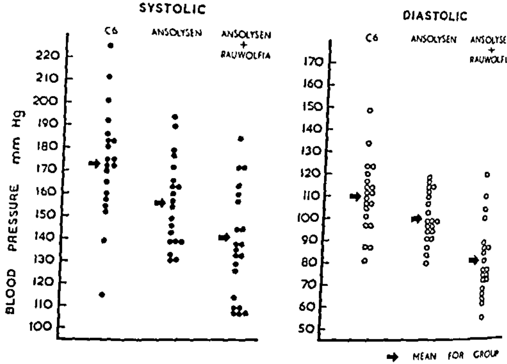



Fig. XX 1
The casual blood pressures (systolic) at an outpatient clinic of 20 patients on (i) hexamethonium ($C_6$) injections, (ii) pentolinium (Ansolysen) by mouth, (iii) the combination of pentolinium (Ansolysen) and a Rauwolfia alkaloid.

on ganglion blocking drugs only. An important aspect of the decrease in the variability of the blood pressure is that casual blood pressures at clinic visits, though sometimes deceptive, become much more valuable as an indication of the extent of the control over blood pressure levels (Fig. XX 1), so that the number of all-day tests which we found it necessary to employ was substantially diminished.

Decrease in the requisite doses of ganglion blocking drugs reduced parasympathetic side effects. This has been noted with the hexamethonium-Rauwolfia combination [6, 10, 22, 39], and also with pentolinium-Rauwolfia [3, 5, 6, 12, 39, 48, 50]. A reduction of side effects is noted not only with the use of reserpine and mixed alkaloidal preparations but also after rescinnamine and canescine [52, 53]. The side effects of chlorisondamine, 139 C 55 and of mecamylamine are also reduced by combining them with the administration of a Rauwolfia alkaloid.

It shot . . . . . .
ed with ... ... be a source of discomfort. Most side effects of Rauwolfia alkaloids are comparatively unimportant but the mental depression, which we have observed with reserpine and to a lesser extent with rescinnamine, but not as yet with canescine, is of supreme importance; and indeed in our clinic we have had much more anxiety with this side effect of Rauwolfia drugs than with any of the side effects of pentolinium or other ganglion blocking substances.

The occurrence of mental depression influences our dosage scheme and choice of a Rauwolfia preparation.

In the early investigations of the use of the combination of a Rauwolfia alkaloid and a ganglion blocking agent Ford and Moyer (1953) employed large doses of Rauwiloid; and we[8, 50] generally used 0.5 mg. of reserpine thrice daily. It is clear to us now that the dose of reserpine which we employed initially, though very satisfactorily from the circulatory standpoint, was too large. The occurrence of mental depression is related to the amount of the drug used, and since we have reduced our routine dose of reserpine from 1.5 to 0 25 or 0.5 mg. daily we have had little trouble with this symptom, and none so far on

on reserpine when transferred to rescinnamine often lost or had a substantial decrease in the degree of cerebral depression. Substantial mental depressions, however, did occur on occasion with rescinnamine. We are at present employing a slightly reduced dose of rescinnamine, usually 0 75 mg daily, and not more than 1 mg. daily. Formerly we used 1.5 mg of rescinnamine daily. Using canescine in doses up to 1 mg daily (it is a rather weaker drug) we have had the typical potentiation of the action of pentolinium, and so far no trouble with mental depression. If we find we can use these lower doses of Rauwolfia alkaloids, particularly canescine and rescinnamine without substantial risk of mental depression, we shall make it our practice to employ them as a routine with pentolinium or another ganglion blocking agent, except in patients who have shown a predisposition to endogenous depression. There are important differences in the action of reserpine, rescinnamine and canescine which make it desirable ... manufacturers ... r preparations. ... a part of the hypotensive activity is due to canescine or rescinnamine, are less likely to induce depression than reserpine administered alone.

Observations by Dustan et al. (1955) showed that subcutaneous as well as alimentary administered doses of ganglion blocking agents have their action increased by the administration of reserpine. Evidently

the effect of reserpine is not due to an increase in gastrointestinal absorption. Our own observations are confirmatory.

Some physicians have been prepared to add a third drug to the combination of Rauwolfia and a ganglion blocking agent. Thus Moser (1955) and Grob (1955) sometimes add hydralazine; Schroeder, Morrow and Perry (1954) add reserpine to their régime of a ganglion blocking agent and hydralazine in cases where the degree of reduction in the blood pressure has not been satisfactory. Agrest and Hoobler (1955) sometimes use a dose of protoveratrine at night because its hypotensive action is not dependent on posture. Kirkendall and Culbertson (1955) usually employ a salt free régime in addition to the drugs. Franklyn (1955) describes his personal experiences in the treatment of high blood pressure and lays emphasis on the usefulness of salt deprivation in conjunction with ganglion blocking drugs and reserpine.

A number of tablets have become available containing both Rauwolfia alkaloids and ganglion blocking drugs. Such preparations are pharmacologically unsound, because, to give a high dose of the ganglion blocking drug may involve having an excessive dose of Rauwolfia alkaloids, with a risk of mental depression. Low dose patients may not obtain the full benefit of potentiation of the desired actions of the ganglion blocking drug because the dose of Rauwolfia alkaloid is too small. We have a strong preference for a fixed dose of Rauwolfia alkaloid with independent adjustment of the dose of the ganglion blocking drug, according to the needs of the individual patient.

## RAUWOLFIA ALKALOIDS AND HYDRALAZINE

Wilkins and Judson (1953) were responsible for introducing this combination and remarked that the effects were additive and possibly were synergistic. Hughes et al. (1955) have reported that the side effects of hydralazine are reduced by combination with reserpine but they prefer the hexamethonium-reserpine combination to hydralazine-reserpine. Corcoran (1954) and Grob (1955) find that the tachycardia of hydralazine is reduced by Rauwolfia. Talso (1955) tries Rauwolfia and hydralazine before using Rauwolfia and pentolinium — he uses the latter when the former does not produce adequate falls of blood pressure. Lee et al. (1956) used reserpine in combination with hydralazine in doses of 300 mg. or less. They found that the range of usefulness of hydralazine was increased by restriction of the dose. They usually avoided toxic reactions. Naegele et al. (1955) also found the combination satisfactory in mild and moderate hypertension but inadequate in severe or renal hypertension. Gaunt et al. (1955) studies the effect of reserpine in combination with hydralazine on hypertension in rats induced by DOCA and salt. They find the mortality is appreciably reduced and the development of periateritis nodosa lesions is prevented. Poimailloux et al. (1956) also report favourable results from the combination of Rauwolfia alkaloids and hydralazine.

## RAUWOLFIA ALKALOIDS AND VERATRUM ALKALOIDS

Wilkins (1952) was chiefly responsible for introducing the combinations of Rauwolfia alkaloids with either hydralazine or veratrum alkaloids. Since the papers by Wilkins much attention has been given to these and other combinations. Voskian et al. (1956) administered parenterally a mixture of 0.1 mg. protoveratrine, 0.5 mg. of cryptenamine and 2.5 mg. reserpine. They consider the combination has advantages but the blood pressure falls which they obtained were not impressive. Corcoran (1954) had little success with veratrum alkaloids alone or in mixtures with other substances. We also had no success with the combination of veratrum alkaloids and Rauwolfia alkaloids but we have always required considerable blood pressure reductions, to normal or near normal in the trough of the blood pressure fall; perhaps, had we been content with small falls of blood pressure, the addition of veratrum alkaloids would have been regarded as successful in certain cases. When only small blood pressure falls are induced it may happen that effective drugs are being given in placebo doses.

## THE HYDRALAZINE-GANGLION BLOCKER COMBINATION

Freis in 1951 was the first to recommend the use of a combination of hydralazine and hexamethonium. Schroeder in 1951 and 1952 published accounts of his experience with this combination and in his subsequent work with Morrow, Perry and others has been largely responsible for developing it.

It seems to be generally recognized that in patients whose blood pressures are not controlled satisfactorily by oral hexamethonium alone, an additional fall of blood pressure may be obtained if sufficiently large doses of hydralazine are given [11, 17, 20, 23, 28, 30, 33, 34, 40, 41, 42].

The combination of hydralazine and pentolinium has also been used. Schroeder (1954) finds that in this type of combination pentolinium has a slight advantage over hexamethonium. Agrest and Hoobler (1955) however, rarely obtained useful additive effects by combining hydralazine and pentolinium. They preferred pentolinium with reserpine. Grimson et al. (1952) state that they found no added reduction of blood pressure or relief of symptoms on using hydralazine in combination with hexamethonium. Rast and Orgain (1955) obtained better results with the combination of hexamethonium and hydralazine than with hexamethonium alone. They also used rigid salt restriction. They obtained reversal of the malignant phase of hypertension in 8 out of 9 instances but consider that the late toxic effects of hydralazine limit its usefulness.

We had no success with the combination of hydralazine and hexamethonium. We were able to induce additional falls of blood pressure

by adding hydralazine to a methonium régime but the doses of hydralazine which succeeded in doing this led to intolerable side effects in most patients. Evidently much depends on the precise technique employed.

Several authors have commented on the increase in the cardiac output and the occurrence of tachycardia when hydralazine alone is administered and have noted that these effects are largely removed when hexamethonium is given in combination with the hydralazine [4, 21, 32, 43].

Schroeder (1954) and Schroeder, Morrow and Perry (1954) have reviewed their experience with the combination of hexamethonium and hydralazine. It appears from Schroeder's recent account of treatment that his patients are rather miserable in the early stages of treatment and he has to encourage them to keep up with it. The régimes we have used from 1950 onwards have usually given relief and added comfort almost from the outset in cases with substantial hypertensive symptoms, and the situation has improved since we used the Rauwolfia-pentolinium combination. It may be for this reason that when we made an attempt to use hydralazine in combination with hexamethonium our patients for the most part preferred even repeated injections to persistence with the side effects of hydralazine.

Schroeder's results are very good so far as relief of hypertensive manifestations are concerned. He and his co-workers emphasize as we do the need for close control over the blood pressure level.

[illegible]

but they used the term somewhat differently from most other authors in that they included cases without papilloedema. However, 92 of their patients had grade 4 retinal changes and would be accepted by most physicians as cases of malignant hypertension. All uraemic cases died. Excluding the uraemic cases [illegible]

of the régime.

Schroeder seems to have duplicated our experience (Smirk and Alstad, 1951) that the death rate is high in patients who stop treatment.

Perry and Schroeder (1955) state that they continue to find hydralazine is necessary in the most severe cases of hypertension. We find very few patients whose blood pressures cannot be controlled by either pentolinium alone or pentolinium in combination with a Rauwolfia alkaloid. Apart from the occurrence of uraemia or of a cerebral vascular accident which makes supervision impracticable it is seldom now that either we or the patients abandon therapy.

## OTHER DRUG COMBINATIONS

Gill, Duncan and Reinhardt (1953) found that dibenzyline administered alone by mouth was not a satisfactory hypotensive agent, but in some patients the combination of sodium restriction with dibenzyline caused a useful reduction in the blood pressure level. Duncan (1954) found combinations of Rauwolfia (crude root) 25 mg., phenoxybenzamine (dibenzyline) 5 mg. and protoveratrine 0.2 mg. ("RDP") of great value in the treatment of hypertension of intermediate severity. He uses Rauwolfia and pentolinium in severe cases.

Corcoran (1954) finds that the tachycardia from adrenergic blockers [illegible] Rauwolfia alkaloids. [illegible] lfia. [illegible] the drug was used in combination with Rauwolfia, the average daily dose was less than 70 mg. per day, whereas, in a previous study, when dibenzyline was used alone the average dose was 669 mg. per day for an equivalent blood pressure response. They think that the main blood pressure fall comes from the dibenzyline, but at a much reduced dose. When protoveratrine was used also there seemed to be comparatively little additional action. Although dibenzyline had been discarded from their clinic, because of the high incidence of side reactions, it appears now that the substance in combination with Rauwolfia can be useful. In the case of dibenzyline, they have not had trouble with parasympathetic side effects. The chief side effects encountered in the Rauwolfia-protoveratrine-dibenzyline combination were nasal congestion, sedation and fatigue, increased appetite, dizziness and slowing of the pulse.

Hood (1956) uses hydralazine in combination with pentolinium and Rauwolfia alkaloids, but seldom uses more than 400 mg. daily of hydralazine. In about 400 patients receiving this drug he has seen one case of a lupus erythematosus-like syndrome, two cases with moderate [illegible]

Conner and McConn (1956) found that patients could often tolerate larger doses of protoveratrine without emesis when given chlorpromazine [illegible]

[illegible] tolinium, but no additional action was noted. Eiber (1955) recommended 25 mg.

by adding hydralazine to a methonium régime but the doses of hydralazine which succeeded in doing this led to intolerable side effects in most patients. Evidently much depends on the precise technique employed.

Several authors have commented on the increase in the cardiac output and the occurrence of tachycardia when hydralazine alone is administered and have noted that these effects are largely removed when hexamethonium is given in combination with the hydralazine [4, 21, 32, 43].

Schroeder (1954) and Schroeder, Morrow and Perry (1954) have reviewed their experience with the combination of hexamethonium and hydralazine. It appears from Schroeder's recent account of treatment that his patients are rather miserable in the early stages of treatment and he has to encourage them to keep up with it. The régimes we have used from 1950 onwards have usually given relief and added comfort almost from the outset in cases with substantial hypertensive symptoms, and the situation has improved since we used the Rauwolfia-pentolinium combination. It may be for this reason that when we made an attempt to use hydralazine in combination with hexamethonium our patients for the most part preferred even repeated injections to persistence with the side effects of hydralazine.

Schroeder's results are very good so far as relief of hypertensive manifestations are concerned. He and his co-workers emphasize as we do the need for close control over the blood pressure level.

[illegible]
advanced hypertension The cases were described as [illegible] but they used the term somewhat differently from most other authors in that they included cases without papilloedema However, 92 of their patients had grade 4 retinal changes and would be accepted by most physicians as cases of malignant hypertension All uraemic cases died. Excluding the uraemic cases [illegible] treated for periods of fifteen to [illegible]
of the régime.

Schroeder seems to have duplicated our experience (Smirk and Alstad, 1951) that the death rate is high in patients who stop treatment.

Perry and Schroeder (1955) state that they continue to find hydralazine is necessary in the most severe cases of hypertension. We find very few patients whose blood pressures cannot be controlled by either pentolinium alone or pentolinium in combination with a Rauwolfia alkaloid. Apart from the occurrence of uraemia or of a cerebral vascular accident which makes supervision impracticable it is seldom now that either we or the patients abandon therapy.

10 Ford, R. V., and Moyer, J. H. Preliminary observations of Rauwiloid-hexamethonium combined therapy of hypertension. Amer. Heart J., 46: 754, 1953.
11 Freis, E. D Methonium compounds in hypertension. Lancet, 1: 909, 1951.
12 Freis, E. D. Recent developments in the treatment of hypertension. Med. Clin. N. Amer., 38: 363, 1954.
13 Freis, E. D., and Wilson, I. M. Effects of mecamylamine in hypertensive patients. Circulation (N.Y.), 12. 707, 1955.
14 Gaunt, R., Antonchak, N., Miller, G. J., and Renzi, A. A. Effect of reserpine (Serpasil) and hydralazine (Apresoline) on experimental steroid hypertension. Amer. J. Physiol., 182: 63, 1955.
15 Gifford, R. W., Jr., Allen, E. V., and Birkhead, N. C. Pentapyrrolidinium bitartrate (M & B 2050A) in the treatment of hypertension: [illegible] Proc. Mayo Clin., 29: 496, 1954.
16 Gill [illegible]
17 Grimson, K. S. Hexamethonium salts alone or with [illegible] regitine for patients with hypertension. J. clin. Invest., 31. 634, 1952.
18 Grimson, K. S. Drugs recently introduced for hypertension. J. Amer. med. Ass., 158: 359, 1955.
19 Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr., and Sieber, H. A. Caution with regard to use of hexamethonium and "Apresoline". J. Amer. med. Ass., 149. 215, 1952.
20 Grob, D. Management of the patient with primary "essential" hypertension. J. Chronic Dis., 1. 546, 1955.
21 Hoobler, S. W. The modern treatment of hypertension. Bull. Amer. Soc. Hosp. Pharm., 11. 23, 1954.
21a Hood, B. The problem of blood pressure reduction in cases with advanced vascular damage. Personal communication, 1956.
22 Hughes, W. M., Dennis, E., and Moyer, J. H. Treatment of hypertension with oral reserpine alone and in combination with hydralazine or hexamethonium. Amer. J. med. Sci., 229. 121, 1955.
23 Johnson, R. L., Freis, E. D., and Schnaper, H. W. Clinical evaluation of 1-hydrazinophthalazine (C-5968) in hypertension. With special re-[illegible] Circulation [illegible]
24 [illegible] west Med. Surg., 4. 789, 1950.
25 Kirkendall, W. M., and Culbertson, J. W. Management of systemic arterial hypertension. Arch. intern. Med., 95. 601, 1955.
25a Lee, R. E., Seligmann, A. M., Goebel, D., Fulton, A., and Clark, M. A. Reserpine-hydralazine combination therapy of hypertensive disease, with hydralazine in doses generally below the "toxic range". Ann. intern. Med., 144. 456, 1956.
25b Luthy, E., and Stucki, P. Die ambulante Behandlung Hochdruckkranker mit Serpasil sowie mit Serpasil-Nepresol. Schweiz. med. Wschr., 86: 831, 1956.
26 McC[illegible] renal hypertensive dogs. Amer. J. med. Sci., 226: 632, 1953.
27 Mason, A. A., and Pelmore, J. F. Combined use of hexamethonium bro

of chlorpromazine and 50 mg. of Rauwolfia root thrice daily. He thought the combination was useful and encountered no jaundice among his 350 patients. Mason and Pelmore (1953) and Aserman (1953) found that procaine amide enhanced the hypotensive action of hexamethonium and assisted effective control of the blood pressure in neurosurgery. The combination is not in use as a treatment for hypertension. Stonehill (1956) finds a slightly greater fall of blood pressure when mannitol hexanitrate is given as well as Rauwolfia alkaloids In angina cases with hypertension we have added long acting organic nitrates (e g. peritrate) to the hypotensive régime in some cases. The conventional doses, useful for the relief of [illegible] sive action. Morrell and [illegible] st blood pressure control [illegible] (1956) find that chlor[illegible] decreases the emetic action of protoveratrine, but insufficiently to permit improved control over the blood pressure level. Luthy and Stucki (1956) treated 83 hypertensives with Serpasil or with Serpasil and Nepressol (a chemical relative of hydralazine). Most patients had a fall of blood pressure with Serpasil but there was little further improvement when the combination with Nepressol was used

## References


1 Agrest, A , and Hoobler, S W. Long-term management of hypertension with pentolinium tartrate (Ansolysen). J. Amer. med. Ass., 157: 999, 1955.

2 Aserman, D. Controlled hypotension in neurosurgery with hexamethonium and procaine amide. Brit med J , 1. 961, 1953.

3 Bain, C W. C , Ashton, F., and Jones, B P The treatment of essential hypertension with pentolinium tartrate combined with Rauwolfia alkaloids. Brit. med. J., 1: 817, 1955.

3a Bartorelli, C. Le traitement prolongée de l'hypertension essentielle avec hexaméthonium et serpasil Acta med scand , suppl. 312: 238, 1956.

3b Conner, P K , Jr , and McConn, R. G. Alleviation of toxic effects of veratrum by chlorpromazine in treatment of hypertension. Fed. Proc , 15: 411, 1956.

3c Conner, P. K , Jr., McConn, R. G., and Moyer, J H. An attempt to alleviate the emetic effect of protoveratrine by the concurrent use of chlorpromazine in the treatment of hypertension. Amer. Practit. (Philad ), 7: 1127, 1956

4 Corcoran, A. C. Advances in treatment of severe hypertensive disease. J. Iowa St. med. Soc , 44· 457, 1954

5 Doyle, A. E , McQueen, E. G , and Smirk, F. H. The combination of reserpine (Serpasil) and pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium) bitartrate (Ansolysen) for the control of high blood pressure. Proc Univ Otago med Sch 32· 4, 1954

6 [illegible] rk, F H Treatment of hypertension [illegible] n combination with pentapyrrolidinium [illegible] ination with veratrum alkaloids. [illegible]

7 [illegible] e Amer Coll. Physic , September 23, 1954.

8 Dustan, H. P , Corcoran, A. C , Schneckloth, R , and Page, I H. Combination therapy of severe hypertension with ganglion blockers and reserpine Circulation (N.Y.), 12· 698, 1955.

9 Eiber, H. B. Combined chlorpromazine-rauwolfia serpentina therapy in essential hypertension — Preliminary report J Amer med. Ass , 158: 730, 1955.

control of hypertension by hyphex. V. Effects on the course of the malignant stage. Circulation (N.Y.), 10: 321, 1954.

46 SINGH, I. Reserpine in hypertension. Brit. med. J., 1: 813, 1955.

47 SMIRK F H. Unpublished observations.

48 [illegible]

49 [illegible]

50 [illegible] 159, 1954

51 SMIRK, F. H., and HAMILTON, M Action of "Ecolid" in man. Brit. med. J., 1: 319, 1956

52 SMIRK, F H, and MCQUEEN, E. G. Comparison of rescinnamine and reserpine as hypotensive agents Proc Univ. Otago med. Sch., 33: 10, 1955a.

53 SMIRK, F. H, and MCQUEEN, E G Comparison of rescinnamine and reserpine as hypotensive agents. Lancet, 2: 115, 1955b.

53a STONEHILL, S. A comparative study of the treatment of essential hypertension Arch intern Med, 97: 189, 1956

54 TALSO, P J The management of hypertensive disease Chicago med. Soc. Bull., June 5th, 1955

54a VOSKIAN, J, ASSALI, N S, and NOLL, L. Hemodynamic effects and clinical application of a mixture of veratrum and Rauwolfia alkaloids. Surg. Gynec Obstet, 102 37, 1956

55 WILKINS, R W New drug therapies in arterial hypertension. Ann. intern. Med, 37, 1144, 1952

56 WILKINS, R W, and JUDSON, W E The use of Rauwolfia serpentina in hypertensive patients New Engl J Med, 248: 48, 1953.

mide and procaine amide in controlled hypotension. Brit. med. J., 1: 250, 1953.

28 MAXWELL, R. D. H., and HOWIE, T. J. G. Ecolid: A new hypotensive agent. Brit. med. J., 2: 1180, 1955.

28a MORRELL, R. M., and HITZROT, J. M. Hypertension of renal origin responding to chlorpromazine and Rauwolfia: Report of case. Angiology, 7: 243, 1956.

29 MOSER, M. Evaluation of drug therapy of hypertension; experience with Ansolysen, hexamethonium, Apresoline, and reserpine. N. Y. St. med. J., 5: 1909, 1955

30 MOSER, M., and MATTINGLY, T. W. I. Critical evaluation of drug therapy of hypertension Postgrad. Med, 17: 351, 1955.

31 MOYER, J. H., HUGHES, W., DENNIS, E., BEAZLEY, H. L., and McCONN, R. Results with a combination of Rauwolfia and adrenergic blockade in the treatment of hypertension. Amer. J. med. Sci, 230: 33, 1955

32 MOYER, J. H., HUGGINS, R. A, and HANDLEY, C A. Further cardiovascular and renal hemodynamic studies following the administration of hydrallazine (1-hydrazinophthalazine) and the effect of ganglionic blockade with hexamethonium on these responses J. Pharmacol, 109: 175, 1953.

32a NAEGELE, C. F., ROSENMAN, R. H., HOFFMAN, C L, and FRIEDMAN, M. Combined Rauwolfia-hydralazine therapy of hypertensive patients. Circulation (N.Y), 11: 182, 1955.

33 NEUMAYR, A. Prinzipien der Hochdrucktherapie Wien Z inn Med, 34: 155, 1953.

34 ORGAIN, E S. Drug therapy for hypertension. Postgrad Med, 17: 318, 1955.

35 PAGE, I. H Treatment of essential and malignant hypertension J. Amer. med Ass, 147· 1311, 1951

36 PATTON, E W J. Tenn St med Ass, 48, 251, 1955

37 PERRY, H. M., Jr, and SCHROEDER, H A The use of pentolinium tartrate with and without hydralazine in the treatment of severe hypertension *New Engl. J. Med., 252, 1057, 1955*

37a POUMAILLOUX, M, CALLEROT, L, and GRANIER, J Étude critique des hydrazinophtalazines Arch mal. Coeur, 49, 351, 1956

37b RAST, C L, and ORGAIN, E S Newer drugs in the treatment of hypertension. Use of hexamethonium in combination with hydralazine Circulation (N.Y), 12, 301, 1955

38 RESTALL, P A, and SMIRK, F H The treatment of high blood pressure with hexamethonium iodide N. Z med J, 49 206, 1950

39 RIVEN, S S The use of drugs in the management of hypertension J Tenn med Ass, 48· 243, 1955

40 ROMNEY, R. B, BULLINGTON, R H, ABILDSKOV, J A, RAY, C T, and BURCH, C E A preliminary report on clinical experiences with hexamethonium and Apresoline in the treatment of diastolic hypertension J Louisiana med Soc, 105 153, 1953

41 SCHROEDER, H. A The effect of 1-hydrazinophthalazine and hexamethonium on hypertension J Lab clin Med, 38 949, 1951

42 SCHROEDER, H. A Control of hypertension by hexamethonium and 1-hydrazinophthalazine Arch intern Med., 89· 523, 1952

43 SCHROEDER, H A Management of arterial hypertension Amer J Med, 17: 540, 1954

44 SCHROEDER, H. A. Hypertensive vascular disease Therapy with modern drugs and its limits J Chronic Dis, 1: 497, 1955

45 SCHROEDER, H. A, MORROW, J. D, and PERRY, H. M Studies on the

by hypotensive
objective changes.
ed reports about
mortality, and changes in objective manifestations, come from those who do not use ganglion blocking agents, but employ Rauwolfia drugs alone, veratrum alone, hydralazine alone, or a combination of these which does not include a ganglion blocking drug. The results obtained in our clinic represent, in most cases, the effects of using ganglion blocking agents alone and in various combinations.

Soon after the introduction of these drugs it became *evident to us* that their use a
ing with malig
asthma [31, 32], (
have survived two years.

## Mortality According to Retinal Grade

Morrison (1953) from McMichael's clinic refers to the return to a reasonably active life of 4 out of 7 patients with malignant hypertension for periods of three, seven, nine and fifteen months. Rosenheim (1954) gave his results in 24 cases of malignant hypertension. Five out of 8 patients with good renal function survived one year, and 3 out of 5 survived two years. When renal function was impaired 3 out of 10 patients survived one year and none out of 4 survived two years. Schroeder (1954) includes as "malignant hypertension" some patients without papilloedema, but in the group as he defines it there was an appreciable diminution below the expected mortality of untreated cases His patients were treated with a combination of hydralazine and hexamethonium for periods of thirteen to thirty-four months.

McMichael and Murphy (1955) consider that the life extension in their series is now statistically significant. Burnett and Evans (1955) had 14 survivors among 22 grade 4 patients treated for four to thirty-one months.

Our series includes 47 patients with malignant hypertension treated for periods up to six years. All malignant hypertension patients coming to our medical service were treated, irrespective of the stage of the disorder Therefore, a few patients were included who were almost moribund When we compare our treated group (all grade 4 cases) with the Keith-Wagener curve an extension of life is apparent (Fig. XXI 1). At four years we have a 58 per cent survival. Several of the patients who died had severe renal disease before starting treatment.

It should be pointed out that ganglion blocking drugs are not being used as a treatment for renal insufficiency, and can only be expected to ameliorate potentially reversible conditions. The prognosis in the renal cases depends mainly on the state of the kidneys and cases of malignant hypertension with renal insufficiency have a poor outlook,

CHAPTER XXI

# RESULTS OF TREATMENT

A clear understanding of the results which are to be obtained by effective methods of treating high blood pressure concerns the subject of pathogenesis as well as the welfare of patients. The demonstration that certain clinical manifestations are removed or greatly relieved by blood pressure reduction supports the idea that hypertension has been the cause of them. If hypertension is the cause, there is good reason to believe that such clinical manifestations can be prevented (I believe they can be) by maintaining the blood pressure at a lower level.

Substantial technical difficulties may be encountered in treating patients with hypertension, and sometimes simple measures leading to small falls of blood pressure have been preferred to more difficult methods (even in severe cases), partly because there were doubts about what could be accomplished by blood pressure reduction, and also because of uncertainty as to whether considerable blood pressure reduction was either necessary or safe. If, however, it can be shown conclusively, and is generally accepted, that there are methods of treating hypertension which decrease mortality, relieve clinical manifestations and allow a more liberal way of living, then technical difficulties will not prevent their adoption.

To speak of the therapeutic use of ganglion blocking drugs without specifying in some detail the manner in which they have been used, gives no clue to the expectation of benefit. The author cannot emphasize too strongly the importance of the technique of therapy; for deficiencies in technique have obscured a simple issue of great practical and theoretical importance, namely, that failures to relieve potentially reversible clinical manifestations in hypertension are almost all iatrogenic.

## MORTALITY IN PATIENTS TREATED BY BLOOD PRESSURE REDUCTION USING GANGLION BLOCKING DRUGS

It has long been my view that improvement in hypertensive manifestations and in the mortality of hypertension depends on effective blood pressure reduction and not on the drug used for the purpose.

vised more closely than those in grade 3; deviations from the régime were treated more seriously, and grade 4 patients when necessary were told frankly how much depended upon adherence to the régime. In contrast, once exudative retinal changes had disappeared in grade

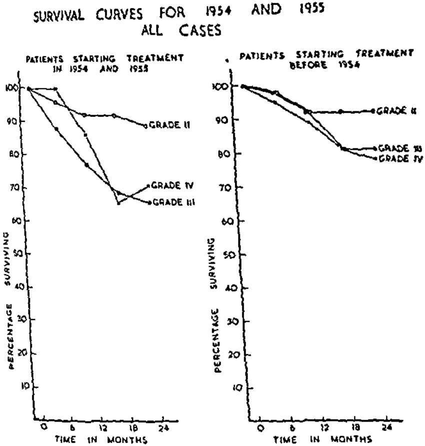



Fig XXI 2a, b

Survivals during 1954 and 1955 in a New Zealand series of patients treated by ganglion blocking drugs together sometimes with Rauwolfia alkaloids

3 patients, we tended not to distinguish them from our grade 2 patients It is now quite clear that patients who have had a grade 3 retinopathy are more liable to develop a fatal illness — usually a stroke — than patients with grade 2 retinopathy. On clinical examination these ex-grade 3 patients may feel, and appear to be, as well as grade 2 cases

In the last two years control over blood pressure levels has improved with the use of combinations of a Rauwolfia alkaloid with a ganglion blocking drug. Furthermore, we have paid more attention to our grade 3 cases Concurrently there has been a decrease in the mortality in

At two years we had only 44 per cent survivors among the cases with renal insufficiency. Patients with malignant hypertension whose renal function is *good* or but *moderately impaired*, have an improved prospect if the blood pressure is well controlled. Comparing the possible with the actual duration of life on treatment we find that, at one year

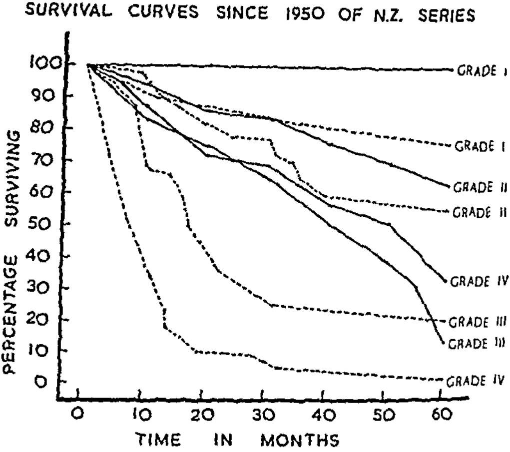



Fig XXI 1

Comparison of survivals in a New Zealand series of patients treated mainly by ganglion blocking drugs (unbroken lines) with the untreated series of Keith, Wagener and Barker (1939) (broken lines) The curves are drawn so as to indicate the percentages of survivors at various times after examination of the patients

out of a possible 32 patients 90 per cent were alive, at two years out of a possible 27 patients 81 per cent were alive, at four years out of 13 patients 61 per cent were alive and at five years out of 8 patients 37 per cent were alive. The results in 1954 and 1955 with improved methods of control over blood pressure levels are seen in Figs. XXI 2 and 3.

In retinal grade 3 cases our results until two years ago were unsatisfactory and are still no better than in our treated grade 4 cases. I attribute this to our taking insufficient care with the treatment of some grade 3 cases. For several years our grade 4 patients were super-

TABLE XXI 1

| | Eye Grade | Life Years | Total Deaths | Cerebral Vascular Deaths | Congestive Heart Failure Deaths | Cerebral Vascular plus Congestive Heart Failure Deaths |
|---|---|---|---|---|---|---|
| Period 1 (Hexamethonium by injection) | 4 | 29.5 | 4 (13.6 %) | 2 (6.8 %) | ½ (1.7 %) | 2½(8.5 %) |
| | 3 | 42.5 | 12 (28 %) | 6 (14 %) | 2 (5 %) | 8 (19 %) |
| | 2 | 67 | 8 (12 %) | 5 (7.5 %) | 0 (0 %) | 5 (7.5 %) |
| | Total | 139.0 | 24 (17.3 %) | 13 (9.3 %) | 2½(1.8 %) | 15½(11.3 %) |
| Period 2 Transition *Period* | 4 | 48.5 | 9 (18.4 %) | 3½(7.2 %) | ½(1.0 %) | 4 (8.3 %) |
| | 3 | 96 | 12 (12.0 %) | 3 (3.1 %) | 2 (2.1 %) | 5 (5.2 %) |
| | 2 | 194 | 15 ( 7.7 %) | 4 (2.1 %) | 1 (0.5 %) | 5 (2.6 %) |
| | Total | 338.5 | 36 (10.6 %) | 10½(3.1 %) | 3½(1.0 %) | 14 (4.1 %) |
| Period 3 Pentolinium combined or *uncombined* with Rauwolfia alkaloids | 4 | 45.5 | 5 (11.0 %) | 2 (4.5 %) | 0 (0 %) | 2 (4.5 %) |
| | 3 | 80.5 | 8 ( 9.9 %) | 1½(1.86 %) | 1 (1.25 %) | 2½(3.11 %) |
| | 2 | 221 | 6 ( 2.8 %) | 4 (1.9 %) | ½(0.25 %) | 4½(2.15 %) |
| | Total | 347.0 | 19 ( 5.5 %) | 7½(2.2 %) | 1½(0.4 %) | 9 (2.6 %) |
| Grand Total | | 824.5 | 79 (9.6 %) | 31 (3.8 %) | 7½(0.9 %) | 38½(4.7 %) |

The totals of grades 4, 3 and 2 should *not be used for* comparative purposes as there are a higher proportion of grade 2 cases in period 3 than in period 1. The top line in the table indicates that in the first treatment period there were 4 deaths in grade 4 cases during 29.5 life-years of treatment, i.e. 13.6 per 100 life years. When ½ a death is set down it indicates that the death was only *partly* due to the disorder.

grades 2, 3 and 4 (Table XXI 1), but the results in grade 3 are still no better than in grade 4. We have reached the conclusion that the grade 3 patients should receive as much supervision as grade 4 cases.

The results of the last two years in grades 2, 3 and 4 patients are shown graphically in Fig. XXI 2. Fig. XXI 2 gives the results in all

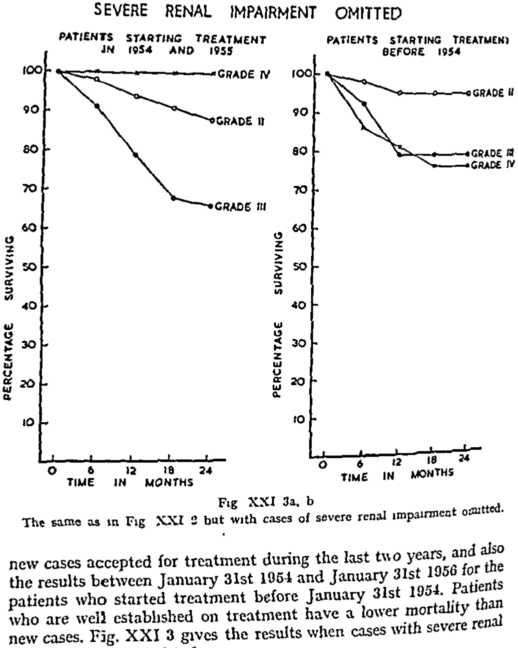



Fig XXI 3a, b

The same as in Fig XXI 2 but with cases of severe renal impairment omitted.

new cases accepted for treatment during the last two years, and also the results between January 31st 1954 and January 31st 1956 for the patients who started treatment before January 31st 1954. Patients who are well established on treatment have a lower mortality than new cases. Fig. XXI 3 gives the results when cases with severe renal impairments are omitted.

Table XXI 1 indicates the improvement in mortality experience in our clinic with better control over blood pressure levels. The percentages express the number of deaths per hundred life years. Where the number of deaths includes a fraction, e.g. half a death from

series of McQueen and Trewin (1952), Harington and Rosenheim (1954), Morrison (1953) and Schroeder (1954), about 7 per cent of deaths were due to congestive heart failure, 30 per cent to cerebral vascular accidents, 20 per cent to uraemia, and 43 per cent of deaths were due to other causes. We have treated about 400 patients during the last six years (not counting those who abandoned treatment) and have had 80 deaths; of these 9.5 per cent were due to congestive heart failure, 39 per cent to cerebral vascular accidents and 51.5 per cent to other causes.

In 1953 [30] it was possible to state that in our Dunedin clinic "for the first few years of treatment, hypertensive heart failure and cardiac asthma as causes of death are almost eliminated by effective methonium therapy." Shirley Smith and Fowler (1955) point out also that there has been a complete change in the mortality pattern in hypertension. They had no deaths from heart failure in their series of 114 hypertensive patients treated with ganglion blocking agents.

A consideration of the causes of death in patients presenting with cardiac asthma, general congestive heart failure, or substantial exertional dyspnoea provides an even more striking illustration of the effect of treatment by ganglion blocking agents upon the outlook of such patients. The death rate among such patients has, unfortunately, been high in our series, 22 patients out of 127 in the course of six years, but only 2 of these patients died from congestive heart failure and in 2 [illegible] .use. The death [illegible] late years with improvement in treatment, but because cerebral vascular accidents are less frequent In 1950 and 1951 the annual percentage mortality was 35 5, in 1952, 1953 and 1954 the percentage was 8. These figures represent the mortality among this group from all causes. This represents a considerable extension of life as the average expectation of life in hypertensive heart failure, without hypotensive therapy, is between one and two years.

## Mortality From Pulmonary Oedema

A problem we have encountered is whether to describe certain patients who have developed pulmonary oedema and died as cardiac or renal deaths or deaths from infection Most were patients with a degree of renal insufficiency or were free from heart failure until an infection developed, usually pneumonia, which caused rapid deterioration. Such cases are not congestive heart failure in the sense in which the term is ordinarily used but inadequacy of the circulation appears to have played a part at the termination. In assigning the cause of death we

congestive heart failure, the half indicates that a death was attributable in part to congestive heart failure, the remaining half being assigned to the other contributory cause. Period 1 refers to our early experience when reliance was placed on hexamethonium by injection. Period 3 refers to our experience from August 1954 to February 1956 with almost all patients on pentolinium alone or in combination with a Rauwolfia alkaloid. Period 2 is the transition period with patients gradually changing over from hexamethonium to more effective régimes. When we compare the mortality in period 3 with the mortality in period 1, we find a decrease in the death rate in each case. The differences are significant for both grade 2 and grade 3 at a 1 in 100 level. The improvement in grade 4 from period 1 to period 3 is not obvious partly because intensive hexamethonium treatment, even in period 1, had secured an appreciable extension of life (see Fig. XXI 1), and also because of a higher proportion of renal deaths in period 3. During period 2 most of the deaths were in patients who were still receiving hexamethonium.

It is evident from Figs. XXI 1, 2 and 3 there is an obvious extension of life in the patients with malignant hypertension. In grades 3 and 2 it is more difficult to discover what the mortality would have been in a similar series of untreated cases, but experience in the last six years shows some slight improvement over the Keith-Wagener series of cases. In the last eighteen to twenty-four months there has been a considerable and statistically significant decrease in the mortality of our grades 2 and 3 cases as compared with our own early experience (Table XXI 1). It seems very likely from these facts, and from the present low mortality, that the mortality of grades 2 and 3 cases is now appreciably lessened by treatment. In grade 3, where our experience has been the least satisfactory, we have had a 66 per cent survival of new cases in the last two years as compared with 36 per cent in the Keith-Wagener series.

A significant fact is that with control over the blood pressure level the usual preponderance of male over female mortality decreased. Taking grades 3 and 4 together the mortality of patients accepted for treatment during the last six years has been 37 per cent for males and 39 per cent for females.

## Mortality in Hypertensive Heart Failure (Left Ventricular and Combined Ventricular)

The proportion of deaths which occur from heart failure in untreated series has been estimated by various authors as between 30 and 60 per cent of all hypertensive deaths, most estimates being in the region of 45 per cent. Even in early accounts of the treatment of hypertension by hexamethonium, congestive heart failure was not prominent as a cause of death. Among 44 deaths collected from the

[illegible] patients who had been under treatment with [illegible]

The present occupational status of our patients with [illegible] hypertension is set out in the following tables.

We have not completed our survey of the occupational status of the patients with retinal grades 2 and 3. However, in 100 consecutive patients attending our hypertensive outpatient clinic we obtained the following results.

| | |
|---|---|
| 1. Leading a productive life (including household duties in women) | 80 |
| 2. Partly or potentially productive | 10 |
| 3. Retired, not substantially incapacitated | 5 |
| 4. Partially incapacitated by conditions arising before treatment started | 5 |
| 5. Partially incapacitated by conditions arising since treatment started | 0 |
| 6. Totally incapacitated | 0 |
| | 100 |

Out of over 300 patients on treatment we know of two who are at present totally incapacitated bed cases. These had had substantial strokes and before starting treatment were regarded as partially incapacitated.

The majority of men whose occupational capacity before treatment was impaired by hypertensive symptoms, have improved their capacity for work or have not deteriorated. The economic gain must be considerable. Several men who thought their working days were over have resumed an occupation and very few of the patients require to be looked after by their relatives. Women on treatment often do less housework and rest more though they are emphatic about their symptomatic improvement. Few, however, are dependent on others. Corresponding results were obtained in the less severe grades of hypertension.

## IMPROVEMENTS IN CLINICAL MANIFESTATIONS

### Retinal Changes

Decrease or disappearance of papilloedema during blood pressure reduction by ganglion blocking drugs alone or in combination with hydralazine or with Rauwolfia alkaloids has been noted by most observers [2, 5, 9, 10, 16, 18, 19, 20, 21, 24, 27, 31, 32, 37]. In some instances authors refer to disappearance of papilloedema in perhaps 50 or 60 per cent of cases. This we regard as an indication of a need to improve the technique of treatment. With no exceptions of which we are aware,

ed with ganglion blocking agents and who deteriorate rapidly and die with pulmonary oedema as a result of renal failure, cessation of therapy or a severe infection.

### Mortality from Cerebral Vascular Accidents

Whereas treatment of only moderate efficiency will diminish the incidence of disability and deaths from hypertensive heart failure, a much better control over the blood pressure levels is required before the incidence of cerebral vascular accidents is decreased to an important extent. In 1950 and 1951 we had a high proportion of deaths from cerebral vascular accidents but in 1954 and 1955 the number of deaths from this cause had diminished, an expression, almost certainly, of better control over blood pressure levels, mainly the result of using pentolinium and later pentolinium in combination with Rauwolfia alkaloids. From the time when we first had a reasonable accumulation of patients we have noted the number on treatment and the mortality in each period of six months. From January 31st 1950 to July 1952 (Period 1 Table XXI 1), hexamethonium by injection was almost the sole method of treatment. From August 1952 to July 1954 (Period 2 Table XXI; 1), some patients were on hexamethonium and some on pentolinium, we call this the intermediate period. From August 1954 to February 1956 (Period 3 Table XXI 1) patients have been on pentolinium; alone or in combination with Rauwolfia alkaloids. The first period represents 139 patient years of exposure to treatment and the third period 347 patient years of treatment. The cerebral vascular deaths in grades 2, 3 and 4 in period 1 were 7.5, 14 and 6.8 per hundred patient years as compared with 1.9, 1.85 and 4.5 per hundred patient years in period 3. These differences are significant at a 1 in 50 level for grade 2, 1 in 100 level for grade 3 and not significant for grade 4. My opinion, therefore, is that the incidence of cerebral vascular accidents in hypertensive patients can be reduced to a significant degree in grades 2, 3 and 4 but only if the régime is satisfactory and adequately supervised. In grade 4 the mortality had been reduced significantly, even in period 1 by intensive treatment, and this minimized the difference between periods 1 and 3. Hood (1956) also has the impression that the incidence of cerebral vascular accidents has been decreased in his series of treated patients.

## EFFECT ON WORKING CAPACITY

Several authors have commented on the improvement in the working capacity of their patients. Campbell, Graham and Maxwell (1952) state: "The most remarkable effect is the return of most of these patients to a state of normal activity either to work or to domestic duties". McMichael (1952) noted an increase in working capacity and Rønnov-Jessen and Bech (1953) found the capacity in work had im-

TABLE XXI 2. (Continued)

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment |
|---|---|---|---|---|---|
| | | Partially Productive | | | |
| 753 | F | Mental defective; left ventricular failure | 31 | Housewife | 34 |
| 775 | F | Left ventricular failure; cerebral vascular accident | 53 | Housewife | 27 |
| 944 | M | Severe left ventricular failure | 50 | Fruit grower | 18 |
| 969 | M | Diabetes; stroke | 48 | Machine knitting | 14 |
| 1024 | F | Major stroke | 44 | Housewife | 7 |
| | | Retired — not seriously incapacitated | | | |
| 53 | M | . . . . . . . . . . . . . . . | 40 | General medical practice 5 years before retiring | 72 |
| 912 | M | Left ventricular failure | 59 | Engineer | 22 |
| 919 | M | Left ventricular failure | 60 | Farmer | 21 |
| | | Incapacitated by conditions arising before treatment started | | | |
| 364 | M | Cerebral vascular accident | 44 | Not working; stroke | 38 |

TABLE XXI 2. *Occupational State of Malignant Hypertension Patients under Treatment* (February, 1956)

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment |
|---|---|---|---|---|---|
| Leading a Productive Life | | | | | |
| 41 | M | . . . . . . . . . . . . . . . . . . | 48 | Accountant | 67 |
| 204 | M | Left ventricular failure | 45 | Railway employee | 56 |
| 207 | M | Left ventricular failure | 57 | Engineer; active | 53 |
| 306 | M | Left ventricular failure; one leg amputated | 55 | Wire-mattress maker | 44 |
| 301 | M | Cerebral accident; recovering from aphasia | 47 | Coppersmith | 42 |
| 382 | M | Encephalopathic attacks | 43 | Garage work | 38 |
| 400 | M | Left ventricular failure | 41 | Priest; educational work | 35 |
| E7 | M | Left ventricular failure | 45 | Farmer | 51 |
| 124 | F | Subarachnoid haemorrhage | 46 | Housewife | 62 |
| 220 | F | Encephalopathic attacks | 63 | Housewife | 56 |
| 357 | F | Left ventricular failure | 52 | Housewife | 40 |
| 734 | F | Aortic incompetence | 30 | Housewife | 34 |
| 755 | M | . . . . . . . . . . . . . . . . . . | 50 | Maltster | 29 |
| 763 | M | Stroke | 45 | Contractor | 28 |
| 781 | M | Blindness left eye | 34 | Garage proprietor | 26 |
| 785 | M | Partial blindness | 34 | Farmer | 26 |
| 967 | M | . . . . . . . . . . . . . . . . . . | 43 | Horticultural instructor | 14 |

TABLE XXI 2 (Continued)

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment |
|---|---|---|---|---|---|
| | | **Partially Productive** | | | |
| 753 | F | Mental defective, left ventricular failure | 31 | Housewife | 34 |
| 775 | F | Left ventricular failure, cerebral vascular accident | 53 | Housewife | 27 |
| 944 | M | Severe left ventricular failure | 66 | Fruit grower | 18 |
| 969 | M | Diabetes, stroke | 48 | Machine knitting | 14 |
| 1024 | F | Major stroke | 44 | Housewife | 7 |
| | | **Retired — not seriously incapacitated** | | | |
| 53 | M | . . . . . . . . . . . . . . | 40 | General medical practice 5 years before retiring | 72 |
| 912 | M | Left ventricular failure | 59 | Engineer | 22 |
| 919 | M | Left ventricular failure | 60 | Farmer | 21 |
| | | **Incapacitated by conditions arising before treatment started** | | | |
| 364 | M | Cerebral vascular accident | 44 | Not working; stroke | 38 |

TABLE XXI 3. *Occupational State of Malignant Hypertension Patients Treated Until Death*

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment | Cause of Death |
|---|---|---|---|---|---|---|
| | | **Leading a Productive Life up to Time of Death** | | | | |
| 123 | M | . . . . . . . . . . . . . . . | 56 | Business executive | 33 | Obstructive jaundice ? cerebral haemorrhage |
| 371 | M | Encephalopathic attacks | 46 | Furnace stoker | 13 | Cerebral haemorrhage |
| 52 | F | Severe heart failure | 47 | Housewife | 14 | Stroke |
| 76 | F | Severe heart failure | 43 | Housewife | 10 | Stroke |
| 161 | F | Two minor cerebral accidents | 32 | Housewife | 28 | Cerebral haemorrhage |
| 716 | F | . . . . . . . . . . . . . . . | 36 | Housewife | 10 | Uraemia |
| 792 | F | . . . . . . . . . . . . . . . | 40 | Housewife | 15 | Uraemia |
| 902 | M | . . . . . . . . . . . . . . . | 48 | Accountant | 15 | Cerebral haemorrhage |
| | | **Leading a Partially Productive Life up to Time of Death** | | | | |
| 51 | M | Congestive failure, low I Q., osteoarthritis | 59 | Worked 2 years on farm; then old men's home, sweeping and cleaning | 48 | Coronary occlusion |
| 336 | M | Minor cerebral accident | 47 | Farmer | 36 | Cerebral haemorrhage |
| 795 | M | Left ventricular failure | 54 | University professor | 9 | Uraemia and stroke |
| 796 | M | Renal insufficiency | 30 | Engineer – fitter | 6 | Cerebral haemorrhage |

TABLE XXI 3. (Continued)

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment | Cause of Death |
|---|---|---|---|---|---|---|
| | | | **Incapacitated Until Time of Death** | | | |
| 49 | F | Severe heart failure and renal insufficiency | 52 | Not working; lassitude | 31 | Bilateral pneumonia |
| | | | **Died in Hospital without Making Substantial Progress** | | | |
| 206 | M | . . . . . . . . . . . . | 48 | In hospital | 0 | Congestive heart failure; suburaemic state |
| 227 | M | Uraemia | 44 | In hospital | 2 | Uraemia |
| 337 | F | Diabetes; Kimmelstiel-Wilson disease | 41 | In hospital | 4 | Infection and uraemia |
| | | | **Died from Apparently Unrelated Causes** | | | |
| 40 | M | Heart failure | 52 | Not working; mental confusion | 48 | Senile deterioration and dementia (cerebral arteriosclerosis) |

TABLE XXI 3. *Occupational State of Malignant Hypertension Patients Treated Until Death*

| Case No | Sex | Additional Clinical Features before Treatment | Age Starting Treatment | Occupation during Treatment | Months Survived on Treatment | Cause of Death |
|---|---|---|---|---|---|---|
| | | **Leading a Productive Life up to Time of Death** | | | | |
| 123 | M | . . . . . . . . . . . . . . | 56 | Business executive | 33 | Obstructive jaundice ? cerebral haemorrhage |
| 371 | M | Encephalopathic attacks | 46 | Furnace stoker | 13 | Cerebral haemorrhage |
| 52 | F | Severe heart failure | 47 | Housewife | 14 | Stroke |
| 76 | F | Severe heart failure | 43 | Housewife | 10 | Stroke |
| 161 | F | Two minor cerebral accidents | 32 | Housewife | 28 | Cerebral haemorrhage |
| 716 | F | . . . . . . . . . . . . . . | 36 | Housewife | 10 | Uraemia |
| 792 | F | . . . . . . . . . . . . . . | 40 | Housewife | 15 | Uraemia |
| 902 | M | . . . . . . . . . . . . . . | 48 | Accountant | 15 | Cerebral haemorrhage |
| | | *Leading a Partially Productive Life up to Time of Death* | | | | |
| 51 | M | Congestive failure; low I.Q.; osteoarthritis | 59 | Worked 2 years on farm; then old men's home, sweeping and cleaning | 48 | Coronary occlusion |
| 336 | M | Minor cerebral accident | 47 | Farmer | 36 | Cerebral haemorrhage |
| 795 | M | Left ventricular failure | 54 | University professor | 0 | Uraemia and stroke |
| 796 | M | Renal insufficiency | 39 | Engineer – fitter | 6 | Cerebral haemorrhage |

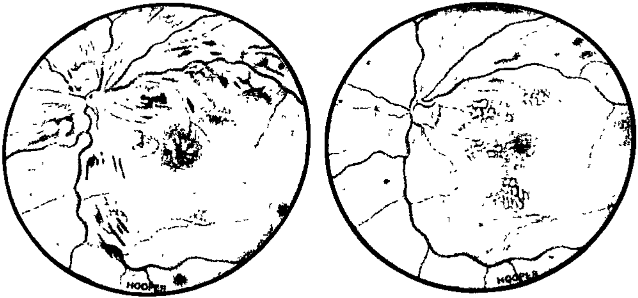



Fig. 6

Drawings of the fundus of a man aged 20 with chronic nephritis and uraemia before and after three months' treatment with hexamethonium

The left hand drawing shows papilloedema, many haemorrhages, soft and hard exudate The right hand drawing shows improvement in the papilloedema and decrease in haemorrhages and soft exudate The hard exudate is more easily seen

Reproduced from Rosenheim M L Brit med J 2 1181 1954

papilloedema has disappeared completely in all patients with malignant hypertension who have been on treatment for six months or more. Should there be doubt about the presence or absence of papilloedema the binocular ophthalmoscope will decide if there is actual elevation of the disc.

Soft exudates clear rapidly, as a rule within one or two months [1, 5, 9, 16, 18, 19, 20, 23, 32]. Hard exudates in our experience (Smirk, 1954) may take as long as twelve months to disperse. Haemorrhages also disappear [1, 5, 16, 18, 20, 23, 28, 32].

It is accepted by all who have treated a substantial group of patients that retinal exudates and haemorrhages disappear in a considerable proportion of cases. It is the view of our clinic that these changes can be relied upon to be removed or greatly reduced in a considerable majority of cases when treatment is adequate. Schroeder (1954) also holds the view that, in every adequately treated case, papilloedema, soft exudates and haemorrhages should clear comparatively quickly and that hard exudates disappear much more slowly.

It is a good working rule for the physician to assume that persistence of any exudative changes in the retina is an indication that treatment is inadequate. A few patients, however, exhibit retinal haemorrhages on very slight provocation and we have one or two patients in whom we have not succeeded in removing retinal haemorrhages despite good control over the blood pressure level. It is possible that these are not hypertensive because in a patient we have observed recently, the haemorrhages have always been confined to the left eye. Such arterial changes as arteriovenous nippings and waist-like constriction of retinal arteries have not been noted to disappear.

## Heart Failure, Cardiac Asthma and Simple Breathlessness

Several observers found that blood pressure reduction relieved hypertensive heart failure, cardiac asthma and breathlessness [6, 9, 10, 11, 15, 16, 19, 22, 23, 25, 29, 32, 35, 36]. A bright spot which illuminated the gloomy experiences of Locket et al. (1952) with methonium compounds, was the observation that a small intravenous dose of M. & B. 1863 produced a most dramatic amelioration of dyspnoea in pulmonary oedema and cardiac asthma. They found the results infinitely more dramatic than with morphine and oxygen. Such results in acute cardiac asthma have often been a source of gratification to the residents in our hospital. The rapid relief of dyspnoea, often with rapid disappearance of râles from the chest is certainly a dramatic event, which has also been commented on by Rosenheim (1952), Ellestad and Olson (1955) and Burch (1955). It is of interest that Bromage (1956) found an increase in the vital capacity of hypertensive heart failure patients after ganglionic blockade.

Special mention must be made of the investigations of Shirley Smith

...commented on the relief of heart failure by ...

Fowler ordinarily use digitalis at the outset but they find that several patients were able to manage without it later.

In our clinic, ... from the outset at discovering whether blood pressure reduct... prolonged rest in bed would ... asthma. It was ... that in the majority of patients these measures sufficed. In ... analyzed our ... asthma. Out of ... tions, 52 were able eventually to remain free from heart failure with blood pressure reduction alone; no digitalis or other ancillary forms of treatment being given. Of the 32 patients with cardiac asthma, but no signs of right ventricular failure, 29 lost their cardiac asthma without requiring treatment with digitalis at any stage. In 1 case digitalis was administered and later discontinued without recurrence of the cardiac asthma, and in 2 cases it was necessary to continue with digitalis administration. There were 40 patients with combined ventricular failure of whom 17 also had cardiac asthma. Of these 40 patients, 13 managed without digitalis at any stage, 9 had digitalis and subsequently discontinued it without recurrence, and 18 required digitalis permanently With few exceptions mercurial diuretics and salt restriction were avoided except in the patients who had to remain on digitalis.

We have always considered that hypertensive heart failure and cardiac asthma patients are much better when they are untreated with digitalis or other ancillary measures; for then they have potent ...

...ures employed in a hypertensive clinic, for if more than one in three or ... ma fail to ... , the tech-... climbing of a flight of approximately 20 steps without appreciable ... efer to the breathlessness, or in younger patients twice this amount. I assume also that male patients of an age suitable for gainful employment will be able to work. Some of these patients will be found to develop congestive heart failure as they grow older for elderly normotensive patients may develop unexplained congestive failure, though not usually cardiac asthma

March 1954 is shown in the Fig. XXI 4. In association with decrease in heart size there is likely to be a marked diminution in the amount

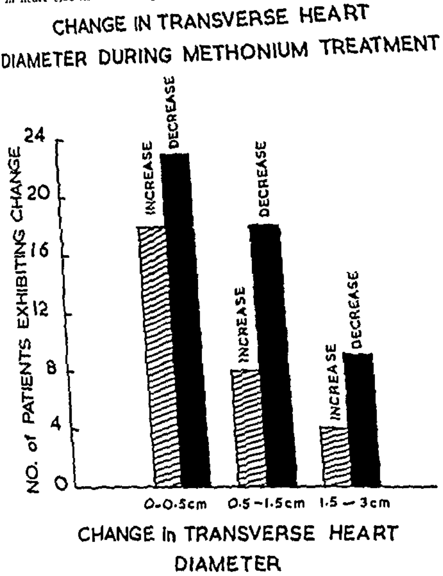



Fig XXI 4

The figure surveys the changes in transverse heart diameter following methonium treatment The number of patients with increase of diameter is shown by hatched columns the number of patients showing decrease is denoted by black columns. (Smirk F H, Brit med J, 1 717, 1954)

of pulmonary congestion in the congestive heart failure cases (Fig. XXI 5, 6 and 7) Smaller decreases in heart size may occur in the absence of heart failure (Fig. XXI 8).

## Heart Failure in Elderly Persons with Slightly Overaverage Blood Pressures

The remarks which have been made so far have reference only to congestive heart failure in patients with substantial hypertension. The dramatic results which we have seen following a diminution in the cardiac overload when the hypertension was considerable, prompted Dr. Hamilton and I to study the effect of reducing the blood pressure in intractable cases of heart failure whose blood pressure was scarcely elevated, being perhaps between 140/90 and 185/110. These are levels of the blood pressure which, although they carry some adverse significance, have not until recently received attention in our clinic. We have now had the experience on many occasions, that reduction of the cardiac overload from levels such as 160/100 to levels such as 120/75 has been associated with an improvement in the state of patients who appeared to have expended the benefits to be derived from digitalis, mercurial diuretics and a salt restricted régime. This has occurred in about half of the patients treated. Though we do not speak of such cases as hypertensive, for their levels may be actually below the average for their age, yet it appears that they are better with a lower blood pressure. We therefore direct attention to the usefulness of decreasing the cardiac load by blood pressure reduction, which in such patients is easily accomplished. Elderly patients, even over eighty years may be treated.

## Pulsus Alternans

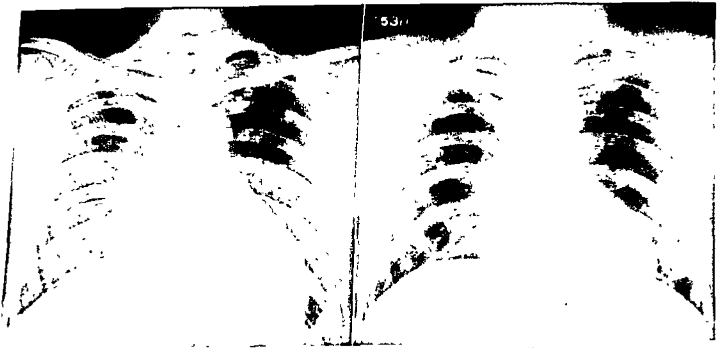
Smirk, McQueen, Doyle and Hamilton[34] made observations on 14 patients with pulsus alternans. The alternans disappeared with treatment but returned temporarily in 1 patient three weeks after stopping digitalis. Not infrequently in the early stages of treatment pulsus alternans will disappear as the blood pressure falls and recur as the blood pressure rises.

## Gallop Rhythm

Often gallop rhythm disappears as the blood pressure falls and recurs as it rises again. The most usual type is a pre-systolic gallop rhythm. In 32 patients who had exhibited gallop rhythm before treatment started, the rhythm was still audible in 15, although all of the 15 were leading an active life, unrestricted by dyspnoea.

## Heart Size

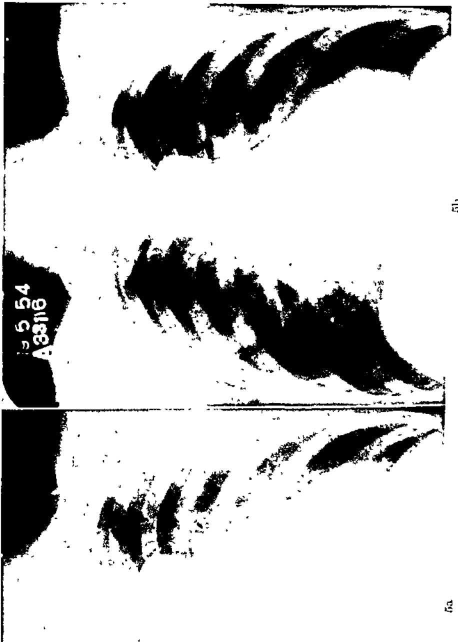
Decrease in heart size was referred to by Restall and Smirk (1950), Campbell et al. (1952), McMichael (1952) and Morrison (1953). While decreases in heart size are not infrequent, they do not invariably occur as was pointed out by Harington and Rosenheim (1954) and Smirk (1954). A figure summarising our experience with heart size up to




6a 6b

Fig XXI 6a, b

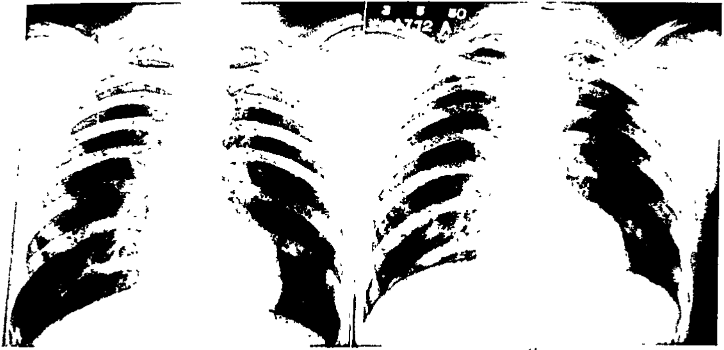
Decrease in heart size and lung congestion in hypertensive heart failure treated by blood pressure reduction (no digitalis, diuretics, salt restriction of prolonged bed rest) 6a — before treatment, 6b — during treatment



5a 5b

Fig. XXI 5a, b

Decrease in heart size and lung congestion in hypertensive heart failure treated by blood pressure reduction (no digitalis, diuretics, salt restriction or prolonged bed rest) 5a — before treatment, 5b — during treatment




8a 8b

Fig. XXI 8a, b

Decrease in heart size in a hypertension patient who was not in heart failure 8a – before treatment, 8b – during treatment



7a 7b

Fig. XXI 7a, b

Decrease in heart size and lung congestion in a breathless male patient with malignant hypertension (no digitalis, diuretics, salt restriction or prolonged bed rest) The patient has an apical lung cyst, left side 7a — before treatment, 7b — during treatment.

a movement in a positive direction in the leads reflecting left ventricular potentials, and decreases in the height of the R waves in most leads (Figs. XXI 9, 10, 11, 12). My colleague, Dr. D. R. Hay, has

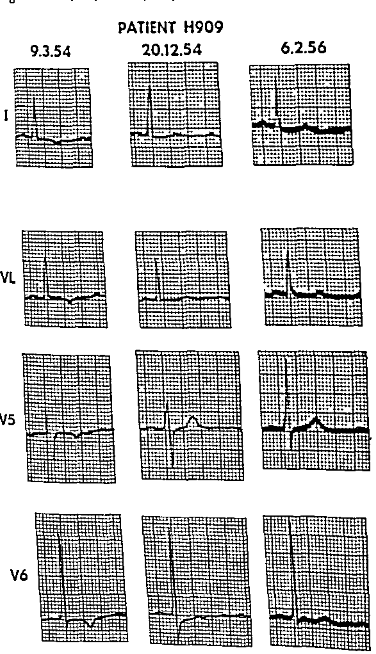



Fig. XXI 10
Improvement in the electrocardiogram during hypotensive therapy.

## Electrocardiograms

Electrocardiographic improvements were noted by Smirk an Alstad (1951); and Doyle (1953) analyzed the Dunedin results in series of 75 patients who had been treated by hexamethonium up to

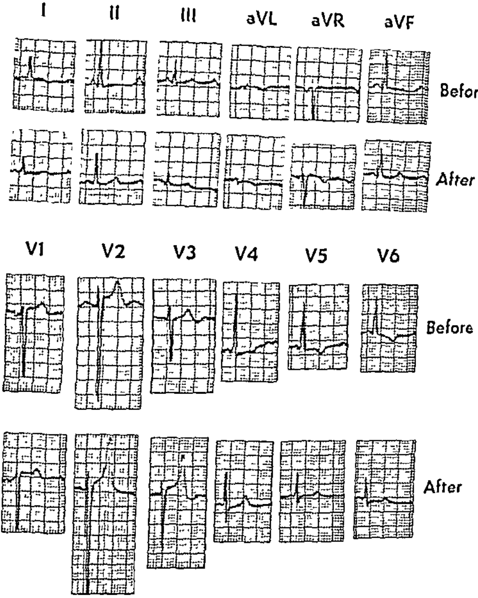



Fig XXI 9

Improvement in the electrocardiogram during hypotensive therapy Note leads I, II, $V_4$, $V_5$, $V_6$

period of three years. Electrocardiographic improvements have also been reported by Palmer (1952), Ronnov-Jessen and Bech (1953), McMichael (1952), Morrison (1953), Moyer et al. (1953) and Schroeder (1954). The kind of improvement which occurs is a return of the ST segment to the isoelectric line, an improvement in the T wave with

followed the electrocardiographic changes in 143 patients who have been on hypotensive drugs for two to six years. Improvement occurred in 47 per cent, 35 per cent remained unchanged and 18 per cent deteriorated.

We have had a number of hypertensive patients with auricular fibrillation and hoped that occasionally we might encounter a return to normal rhythm such as often occurs on the relief of hyperthyroidism, but this has not occurred.

### Angina

Angina pain may be relieved by judicious reduction in the blood pressure level. Alstad and I referred in 1951 to patients who had some decrease of pain on reduction of the blood pressure, but if the blood pressure was reduced too much in these cases pain was provoked. The experience of our clinic in the treatment of 50 hypertensive patients with angina was described by Doyle and Kilpatrick (1954). They found that in about one third of patients treated it was possible to discover a degree of blood pressure reduction which was associated with loss of angina on ordinary effort. Two thirds of the remainder were improved. Where blood pressure reduction alone is insufficient, reduction in the metabolic rate by methyl thiouracil and the use of Peritrate brings a degree of relief to most patients. Such treatment does not seem to involve any special risk of cardiac infarction.

It should be mentioned that the aim in these cases is to avoid reducing the blood pressure below 140 or 145 systolic in the standing posture at the trough of the blood pressure fall. In patients who are frequently exposed to hypotensive blood pressure levels it is likely that cardiac infarction is a distinct risk. Other reports of improvement of anginal pain come from Rønnov-Jessen and Bech (1953), Moyer et al. (1953), Shirley Smith and Fowler (1955), Waldman and Pelner (1956) and Hood (1956).

### Other Clinical Manifestations

Such symptoms as headache and giddiness are regularly relieved by adequate treatment. Patients who have complained of severe [illegible] completely. It is [illegible] as headache and [illegible] patients with hypertension are by no means exempt from neurosis, but it is difficult to believe that the relief of headache without significant recurrence, in periods as long as five or six years from starting treatment, is due to the amelioration of neurosis. Rosenheim (1952) referred to the dramatic relief of intense headache and vomiting in certain hypertensive patients. Campbell, Graham and Maxwell (1952) also noted striking relief. A decrease in the amount of urinary albumin has been noted

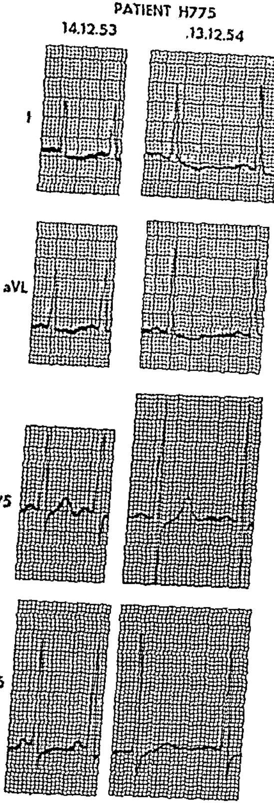



Fig. XXI 11
Improvement in the electrocardiogram during hypotensive therapy.

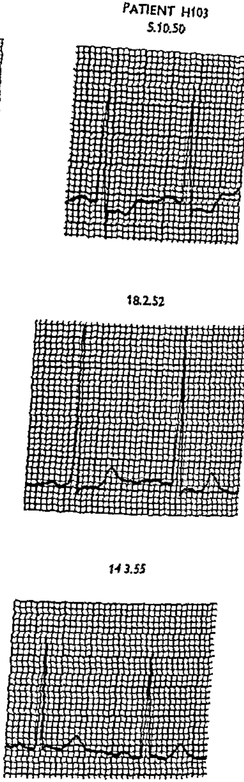



Fig. XXI 12
Improvement in the electrocardiogram during hypotensive therapy Lead I

15 McQUEEN, E. G., and TREWIN, E. Treatment of hypertension with hexamethonium bromide. Med. J. Aust., 2: 425, 1952.
16 MORRISON, B Parenteral hexamethonium in hypertension. Brit. med. J., 1: 1291, 1953
17 MOYER, J. H., MILLER, S. I., and FORD, R. V. Orally administered hexamethonium chloride in hypertension. J. Amer. med. Ass., 152: 1121, 1953.
18 MURPHY, E. A. Treatment of hypertension with hexamethonium bromide. Lancet, 2: 899, 1951.
19 PALMER, A. J. The management of hypertension with hexamethonium bromide. Med. J. Aust., 2: 428, 1952.
20 PLATT, R. Hypertensive retinopathy and its medical treatment. Quart J. Med, n s. 23: 441, 1954.
21 RESTALL, P. A, and SMIRK, F. H. The treatment of high blood pressure with hexamethonium iodide N. Z. med. J., 49: 206, 1950.
22 RØNNOV-JESSEN, V., and BECH, V. Medicamentel behandlung af hypertensio arterialis foreløbig meddlelse om egne erfaringer med hexamethonium. Ugeskr. Laeg, 115: 589, 1953.
23 ROSENHEIM, M. L. Discussion on the medical treatment of hypertension. Proc. roy Soc Med., 45: 269, 1952
24 ROSENHEIM, M. L. The treatment of severe hypertension. Brit med. J, 2: 1181, 1954
25 SAVILLE, S. Pentamethonium in hypertension. Lancet, 2: 358, 1950.
26 SCHROEDER, H A Management of arterial hypertension. Amer. J. Med, 17. 540, 1954.
27 SCHROEDER, H A., MORROW, J. D., and PERRY, H. M, Jr. Studies on the control of hypertension by hyphex. I Effects on blood pressure. Circulation (N Y), 8. 672, 1953.
28 SHAW, G. B Continuous oral hexamethonium in essential hypertension — Further experiences in treatment. Glasg. med. J., 33: 410, 1952.
29 SMIRK, F H Methonium compounds in hypertension Lancet, 2: 477, 1950.
30 SMIRK, F. H Practical details of the treatment of hypertension by hexamethonium salts and by pentamethylene 1:5-bis-n-(n-methyl-pyrrolidinium) bitartrate (M & B. 2050) N Z. med. J., 52: 325, 1953.
31 SMIRK, F H. Results of methonium treatment of hypertensive patients. Brit med J, 1. 717, 1954
32 SMIRK, F. H, and ALSTAD, K S Treatment of arterial hypertension by penta- and hexa-methonium salts Brit. med. J, 1: 1217, 1951.
33 SMIRK, F. H., HAMILTON, M., MCQUEEN, E G, and DOYLE, A. E. Unpublished observations
34 SMIRK, F H, MCQUEEN, E G, DOYLE, A. E, and HAMILTON, M. Unpublished observations
35 SMITH, K S, and FOWLER, P. B S. Prevention and treatment of hypertensive heart-failure by ganglion-blocking agents. Lancet, 1: 417, 1955.
36 SMITH, K S, FOWLER, P B S, and EDMUNDS, V. Hypertension and its control by hexamethonium Brit med J, 2: 1243, 1954.
36a WALDMAN, S, and PELNER, L. Treatment of the ambulatory hypertensive patient with pentolinium tartrate Amer J. med. Sci, 231: 140, 1956.
37 WERKÖ, L, FRISK, A R, WADE, G, and ELIASCH, H Effect of hexamethonium bromide in arterial hypertension. Lancet, 2: 470, 1951.

sometimes (Harington and Rosenheim, 1954), and we have made the same observation.

The future may bring improvements in hypotensive drug therapy which will simplify treatment, success being assured by adherence to the instruction on the wrapping paper. In 1957 our methods of treatment depend for success upon the science and art of the physician and on watchfulness over the progress of patients. The physician counts for more than the drug. Therefore, *the treatment of a group of severe* hypertensive patients becomes a rewarding experience, but reserved for those who are prepared and able to expend time in its application.

## References


1 Barnett, A. J Ocular effects of methonium compounds. Brit. J. Ophthal, 36. 593, 1952.

2 Barnett, A. J, and Fraser, J. R. E. Methonium treatment of arterial hypertensive disease. Alfred Hosp. clin. Repts, 4: 35, 1954.

2a Bromage, P R. Hypotension and vital capacity. Anaesthesia, 11: 139, 1956

3 Burch, R. R. The effects of intravenous hexamethonium on venous pressure of normotensive and hypertensive patients with and without congestive heart failure Circulation (N.Y.), 11. 271, 1955

4 Burnett, C. F. Jr, and Evans, J. A. Drug therapy in hypertension with hemorrhagic hypertensive retinitis. New Engl J. Med., 253: 395, 1955.

5 Campbell, A. J. M, Graham, J. G, and Maxwell, R D. H. Treatment of hypertension by oral methonium compounds. Brit med. J., 1: 251, 1952.

6 Campbell, A., and Robertson, E. Treatment of severe hypertension with hexamethonium bromide. Brit med. J., 2: 804, 1950.

7 Doyle, A. E Electrocardiographic changes in hypertension treated by methonium compounds Amer. Heart J., 45: 363, 1953.

8 Doyle, A. E, and Kilpatrick, J. A. Methonium compounds in the angina of hypertension. Lancet, 1. 905, 1954

8a Ellestad, M. H, and Olson, W. H. The use of intravenous ganglionic blocking agents for acute pulmonary edema. Circulation (N. Y), 12. 701, 1955.

9 Ford, R. V, and Spurr, C. L The treatment of the ambulatory hypertensive patient with hexamethonium administered orally. Amer. Practit. (Philad ), 5: 251, 1954

10 Harington, M., and Rosenheim, M L. Hexamethonium in the treatment of hypertension. Lancet, 1: 7, 1954

10a Hood, B. The problem of blood pressure reduction in cases with advanced vascular damage. Personal communication, 1956.

11 Kelley, R T., Freis, E. D., and Higgins, T F. The effects of hexamethonium on certain manifestations of congestive heart failure. Circulation (N.Y), 7: 169, 1953

12 Lockett, S., Swann, P. G, Grieve, W. S M., and Player, H P M, & B 1863, a homologue of hexamethonium, in treatment of hypertension. Brit. med. J., 1: 254, 1952

13 McMichael, J. The management of hypertension Brit. med. J, 1: 933, 1952

14 McMichael, J., and Murphy, E A Methonium treatment of severe and malignant hypertension. J. Chronic Dis, 1· 527, 1955.

clinics, including our own, found that it was wiser to use only small doses. Under these circumstances mental depression is quite unusual and patients usually feel better and calmer. If, however, a patient feels unaccountably depressed while taking these medicines this should be mentioned to the doctor.

### The Ganglion Blocking Group of Drugs

Some years ago, just one of these drugs — hexamethonium — was available, but in the last few years several more drugs of this group have been discovered. We try to find out which drug suits the individual patient best. There certainly are differences. The drugs we are using in our clinic at the present time are Ansolysen, Ecolid, Presidal and Inversine. Nearly all patients can take these drugs successfully in tablet form, but there are a few patients who require to have injections and they need to learn how to inject themselves.

These ganglion blocking drugs are very effective and can be relied on to decrease the blood pressure. Their main disadvantages are that treatment is not so simple as with Rauwolfia and that there are some side effects which may be a little troublesome for a time.

*Nearly everything in these instructions is concerned with the important* [illegible] *disorder to progress. In order to obtain benefit and at the same time to live comfortably, it is necessary for the patient to be thoroughly familiar with what follows.*

### Differences in the Blood Pressure when the Patient is Lying, Sitting and Standing

When no medicine has been taken the blood pressure is more or less the same no matter what position you are in, but after any of these drugs the blood pressure only falls a little when you are lying flat, falls more when you are sitting, and still more when you are standing. In treating patients we make use of this effect to get a bigger fall of blood pressure with a smaller amount of medicine. *That is why we ask patients on these drugs to remain in the sitting or standing posture throughout the day, and if they desire to rest they should do so sitting on a couch or chair with the head and body well propped up. During the night also we ask patients to sleep in the sitting posture* with many pillows or, better still, with a wooden framework behind the pillows. A bolster is placed under the mattress so as to lift it up under the thigh, and prevent the patient from slipping down in bed during sleep (Fig. XIX 1b).

The dose of the drug is adjusted so as to bring your blood pressure

# APPENDIX 1

## INSTRUCTIONS TO PATIENTS ON TREATMENT FOR HYPERTENSION

(Dunedin Hospital, May 1957)

These instructions may seem at first to be rather involved, but it really is important for you to know something about your complaint, in order to co-operate with us in arranging your treatment. The technicians and doctors will be very glad to help you with any matters on which you need further information or explanation.

. . . . . . . . . . .

The object in treating high blood pressure is to decrease the risk of complications of high blood pressure such as heart failure and stroke and, secondly, to relieve symptoms such as headache and breathlessness in cases where these are due to high blood pressure.

There are a number of drugs used in the treatment of high blood pressure. Two groups of drugs are used in the Dunedin hospital, namely, the Rauwolfia group of drugs and the ganglion blocking drugs. *Almost always, patients will be receiving either one or both of these medicines.*

### The Rauwolfia Group of Drugs

The first group is obtained from an Indian plant — these are called the Rauwolfia drugs. The medicine as obtained from the plant contains a mixture of several pure substances (reserpine, rescinnamine, canescine and others). *Some patients do best with a mixture and others* with single substances, but the actions of all the medicines from the Rauwolfia plant are very similar.

Treatment by the Rauwolfia drugs is easy. The patient simply takes one or more tablets daily according to instructions and visits the Clinic at intervals to make sure that the medicine is having the required effect.

Unfortunately, *only* a few patients get a sufficient decrease of the blood pressure on these drugs alone. It then becomes necessary to change to, or to add, one of the ganglion blocking drugs. The combination of a Rauwolfia alkaloid with a ganglion blocking drug suits many patients very well.

It was thought at one time that Rauwolfia drugs were free from important side effects. When small doses are used this is very nearly true. Large doses, however, may cause *mental depression* and several

what the sensations are like and also you will realize how easily and effectively you can get rid of the symptoms when they occur — for example, at home and if you have no doctor to refer to at the time.

When the blood pressure falls too much the usual symptoms are a feeling of faintness or dizziness, or sometimes a feeling of excessive tiredness and an urgent feeling that one must flop down into a chair or lie down. In some patients these warning signs must be attended to without delay — in other patients there is no harm in trying to be a little tough and not easily giving way to them. The doctor, from the technician's tests, will be able to give you advice about this. In the absence of definite advice to the contrary you should sit down when such symptoms occur and, if they are not promptly relieved, lie down for 10 minutes or for whatever time is necessary. If such symptoms occur after your dose you should always inform your doctor so that he can advise you whether the dose needs a slight reduction. In some patients it is necessary to give a dose which makes it essential for the patient to sit down for 40 minutes to 1 hour at some time after the medicine.

*Side effects and discomforts nearly always diminish in the course of a few months on a good régime,* so that almost all patients who stick to it come to find the treatment less and less troublesome as time goes on. If there is faintness after each dose, or if there is a recurrence of high blood pressure symptoms, then there is a very good chance that the dosage scheme requires revision — either a decrease or an increase in the dosage, sometimes a different spacing between doses.

You may interrupt treatment for a day pending a prompt consultation with your doctor concerning any symptoms which appear to be due to these drugs, but it is imperative to get back on to treat-

[illegible]

*however, to be patient about this as it may take time to make the adjustments.*

The number of deaths and of severe illnesses among untreated cases of the severe type contrasts with the much smaller number of deaths and of complications among patients under effective treatment. In some severe types of hypertension the mortality has been reduced by treatment to one tenth of the mortality of untreated cases. The mortality has also been much less in patients [illegible] areful [illegible] . The [illegible] ice of [illegible] iresome

down to about normal when you are standing. There is a big advantage in this because if by any chance the medicine takes too much effect, and there is faintness or dizziness on standing (because the blood pressure falls rather too low) then in the sitting position the symptoms may be relieved in a few moments. If they are not relieved promptly by sitting or if they start while you are in the sitting position, *then lying flat, especially with the knees raised, will usually disperse any unpleasant effects within a few minutes.*

Because the blood pressure may fall low on standing very still, *patients should avoid getting into situations where they are left standing in a bus or in a queue at a time when under the full action of the medicine.* This is usually within two hours after the injection or tablets, but it varies a little according to drug given and the person taking it. You will soon know by experience what happens in your own case.

Usually your doctor will try to arrange that your blood pressure falls to a level which leaves you substantially comfortable when standing. For some patients it is necessary to give rather larger doses and such patients, especially women at home, usually arrange to occupy themselves at this time with something which allows them to be seated. The effect of different positions on the blood pressure is the basis of the *standing test* which you should know about.

When the doctor regulates your dose he does so with the idea of reducing the blood pressure so that when it reaches its lowest level it still leaves you reasonably comfortable in the standing position. The ideal dose must be judged very accurately because it is only just below the dose which makes you feel a little faint in the standing position. If then you are on tablets, it is a ½ or a ¼ of a tablet below the dose which causes a little faintness when standing. If you are on injections then an accurate tuberculin syringe, graduated in hundredths of a cubic centimeter is necessary, and the dose must be accurate to one of these subdivisions on the syringe. This statement applies both to Ansolysen and to other drugs which have come into use more recently.

It becomes necessary to know what are the effects of doses which are slightly too large.

*If you are wise you will not be frightened by the descriptions of possible side effects which follow. Instead you will realize that to a large extent you can avoid or quickly overcome them if they occur.*

### What Happens When the Dose is a Little too Much for You?

You are bound at times to have doses which prove to be rather bigger than they should be, and it is important to be able to recognize the symptoms which occur when the blood pressure is too low. It is also important to know the very simple and effective measures which can be taken to relieve such symptoms. For this reason we hope, in the

*Side effects.* — Some blurring of the vision and dryness of the mouth are sid [illegible] though, where either of the[illegible] relief. [illegible] but not at other times, can be used. An [illegible] prescribed which lessens the dryness of the mouth.

If there is constipation this can usually be fully corrected with [illegible] or some other suitable purgative. The [illegible] tablets, *do not* take any further injections [illegible] your doctor — you should not delay in this because of the risk attached to uncontrolled high blood pressures.

*Car driving.* — This depends on the effect of the drug on the particular patient. Nearly always when the patient has become stabilized on the drug there is no difficulty with car driving. The blurring of vision does not usually affect the patient for long distance. If the patient is used to the action of the drug and knows he is not liable to faintness on the doses taken, car driving is permissible.

*Parties and social occasions.* — If the patient has any difficulty it is likely to come on if there is a long period of standing which may induce faintness. The patient will probably be comfortable if seated. If it does not happen frequently, the dose of the drug taken prior to the occasion may be reduced slightly Alcohol may be taken in moderation if desired.

*Very hot weather.* — Some patients find that they have to reduce the dose of ganglion blocking drug slightly in hot weather.

*Various illnesses* — Patients should remember that in some illnesses the action of the ganglion blocking drugs becomes too strong and it is necessary to reduce the dose temporarily. This occurs particularly when there is a raised temperature or bad diarrhoea or vomiting.

*Lastly.* — Once you have got your treatment properly adjusted — don't count yourself as a sick person

## APPENDIX 2

### CHECK LIST FOR TREATMENT BY HYPOTENSIVE DRUGS

The answer to all these questions should be "yes". One "no" can explain an inadequate fall of blood pressure or excessive side effects.

1. *Is full use made of posture both during the day and during the night?*

side effects is comparatively small and we feel we can now encourage the few who have important discomforts by relating that, in our experience, those who persist usually find that their troubles lessen or vanish altogether.

## How to Decide if Your Dose is Sufficient

The doses of all these ganglion blocking compounds have to be increased quite frequently in the early stages of treatment because the substances produce rather less effect as patients get used to them. (Inversine is sometimes an exception to this rule). After a few months, however, the dose is usually constant and no further increase is required.

As already mentioned, in the majority of patients there is only a small difference between the dose which is ineffective and the dose which causes a little faintness. This is why it is so necessary to be accurate.

*Reduction of dose.* — There is a useful way of telling whether the dose is approximately correct or not. You will come to recognize the length of time after taking a dose of tablets, or after an injection, when the treatment has its maximum effect upon you. If at this time you feel dizzy or faint or have a sense of undue fatigue, and an urgent desire to flop down, then the dose you are taking is not too small and usually is a little too large. Usually if you have sensations of this kind it is correct to reduce the dose slightly — e.g. by a ¼ or a ½ tablet if you take it by mouth, or by one or two small divisions on the tuberculin syringe if you take it by injection. You can go on reducing the dose in this way until the dizzy feelings become quite trivial. It is important, however, to have the dose as near to the dose which makes you feel a little faint and dizzy as is comfortable.

*Increase of dose.* — If you have none of these sensations it is desirable to increase the dose by such small amounts as are mentioned above until you get the sensations of dizziness, etc. Then you may reduce the dose again until these have just disappeared. By making a trial of the effect of small dose increases you learn whether your dose is high enough.

*The standing test.* — There is a way of deciding if you are very near to the correct dose without increasing the dose. The test (called the standing test) is to stand in front of a clock, quite still without any muscular movement, for a period of exactly one minute. *The test is made at the time when you feel the drug is having its maximum action.* If your dose is correct you are likely, when standing perfectly still, to experience the sensations of slight dizziness referred to above. If you get no dizziness or other sensations with the "standing test" then you should increase the dose until a little dizziness is experienced under these conditions. The explanation of the "standing test" is that with very quiet standing the blood pressure falls to a rather greater extent.

had one patient in which this occurred. Such blood pressure increases can be avoided by suitable sedation or basal anaesthesia. There is room for more work on the problems of anaesthesia in hypertensive patients.

*Nitrous oxide.* Wright and Thompson (1930) attribute the marked rise of blood pressure with pure nitrous oxide anaesthesia to anoxia. The initial rise may be explained by excitement. Apart from asphyxia and excitement they think nitrous oxide has no pronounced effect on blood pressure levels. Haugen (1943) agrees with this and advocates the concurrent use of pentothal sodium (usually 0.25 to 0.50 gm.) to lessen excitement, or of a carbon dioxide absorption unit to avoid the pressor effect of the carbon dioxide. He thinks that with proper management of the anaesthesia, nitrous oxide may be used in hypertensive patients. Clement (1945) finds an elevation of the blood pressure in the ordinary fast method of induction. With nitrous oxide and oxygen the blood pressure was found to return to normal except where there was a degree of asphyxia.

Hypertensives are much more liable to large blood pressure rises than normotensives and most reports make no special reference to results in hypertensive patients. My inclination is to advise against nitrous oxide until more detailed studies become available.

*Cyclopropane* anaesthesia may be accompanied by rises or falls of blood pressure. On stopping anaesthesia the blood pressure may decrease to subnormal levels. Dripps (1947) thinks the blood pressure rises in cyclopropane anaesthesia may be due to carbon dioxide retention. Whitacre and Sankey (1943) also consider that periods of marked hypertension during profound cyclopropane anaesthesia may be related to respiratory depression.

*Tribromethanol* (avertin) leads to falls of blood pressure. Kennedy (1930) found the systolic blood pressure falls range from 2 to 102 mm. Hg, and the diastolic from 0 to 30 mm. Hg. Evidently some of the patients were hypertensive. Taylor and Lund (1932) studied 50 gynaecological cases and reported an average preoperative pressure of 125/65 and, after avertin anaesthesia, an average post-operative pressure of 85/45.

*Barbiturates.*—Thiopental (pentothal) anaesthesia is usually accompanied by a rise in pressure during induction, then the blood pressure tends to fall below the usual range and finally rises slowly again to the original level

*Ether anaesthesia* —There is usually a preliminary rise in blood pressure during the induction of anaesthesia after which the blood pressure is likely to return to normal in the absence of respiratory difficulties.

*Spinal anaesthesia* — It is generally agreed that the falls of blood pressure during spinal anaesthesia are much greater in patients with hypertension than in normotensive persons. Hill (1937) remarks that in patients receiving premedication with 100 mg. ephedrine the blood

2. *Is dosage control in terms of blood pressures taken in the standing posture?*
3. Does the blood pressure (standing) drop to about 120/80 in the trough of the blood pressure fall?
4. Are checks other than the casual blood pressures at clinic visits in use for control of the régime?
5. *If hexamethonium, Ansolysen or Ecolid are used have adjustments been made for the occurrence of drug toleration?* (This is usually unnecessary with Inversine).
6. *Is there indirect evidence that adequate blood pressure falls are being secured during most of the 24-hour day?*
7. Is the dose adjusted to an accuracy of:
   10 to 20 mg. with oral Ansolysen
   5 to 10 mg. with oral Ecolid
   1 mg. with oral Inversine
8. *Are the effects of the ganglion blocking agent usually predictable,* so that the patient feels secure?
9. *Are all potentially reversible hypertensive manifestations,* such as breathlessness, headache, etc. relieved or much improved?
10. *Have routine measures been used as required for the relief of side effects?*
11. In the case of Rauwolfia alkaloids is the daily dose restricted to one of the following:
    0.5 mg. or less of reserpine
    0.75 mg. or less of rescinnamine
    1.0 mg. or less of canescine
    8.0 mg. or less of the alseroxylon fraction
    400 mg. or less of whole Rauwolfia root
12. *Have detailed mimeographed or printed instructions been issued to the patient* and has the patient had the opportunity to ask questions and discuss difficulties?
13. Have arrangements been made for a regular monthly (later even 2-monthly) follow-up visits?

## APPENDIX 3

## ANAESTHESIA IN HYPERTENSIVE PATIENTS

The changes in the blood pressure of hypertensive patients which may be recorded during anaesthesia are not all due directly to the anaesthetic. Excitement during or before the period of induction as well as changes during anaesthesia may cause considerable elevations of the blood pressure and as Haugen (1943) points out, a cerebral haemorrhage in the course of an anaesthetic is not unknown. We have

## General Remarks on Anaesthesia for Hypertensive Patients

More exact observations are needed concerning the effects of anaesthesia in hypertensive patients. Whitacre and Sankey (1943) state that effects upon the blood pressure do not depend only upon the anaesthetic used but upon the method used. *Indeed*, they conclude that it is impossible to say that any one anaesthetic agent is to be preferred for patients with hypertension. Increase or decrease of carbon dioxide, anoxaemia and posture may have important effects. Whitacre and Sankey (1943) point out that changes of posture, such as turning the patient from the dorsal to the ventral position or from the horizontal to the sitting posture, may precipitate marked *falls of blood* [illegible] have even been associated with fatal reactions. The effect

[illegible]

which case it is desirable to arrange for a head-up tilt.

It is probably unwise to risk substantial blood pressure rises as strokes have occurred during operations and acute pulmonary oedema might develop. Moderate blood pressure falls are harmless and usually helpful, but hypertensives unaccustomed to low blood pressures may get symptoms of cerebral anaemia at fully normotensive levels. My [illegible] that apart from neurosurgical cases an ideal level of the [illegible]

[illegible] sive therapy. If reserpine (Serpasil) is being given for the hypertension it need not be omitted in the immediate preoperative period, but if the patient is being treated by hexamethonium, pentolinium (Ansolysen) or other ganglion blocking drugs it is wise, in most patients, to stop administration the night before the operation. As soon as the blood pressure begins to rise again treatment will be resumed at a third to two-thirds of the preoperative dosage level, and the dose will be adjusted daily to maintain adequate blood pressure reduction.

### References


1 Burch, J C, and Harrison, I R The effect of the administration of fluid on the fall in blood pressure caused by spinal anesthesia. Arch. Surg. (Chicago) 22 1045 1931

2 [illegible]

3 [illegible] siology, 8 15, 1947

4 Gregory, R, and Levin, W C Studies on hypertension: Effect of high spinal anesthesia on the blood pressure of patients with hypertension and far-advanced renal disease — its possible relationship to the pathogenesis of hypertension J. Lab clin. Med, 30: 1037, 1945.

pressure, when the spinal anaesthesia has been induced, may be found to have fallen or risen. After the peritoneum was opened, however, the blood pressure fell in every case.

Gregory and Levin (1945) observe that the blood pressure falls during spinal anaesthesia occur in patients with advanced renal disease as well as in patients with essential hypertension. Burch and Harrison (1931) and Walker (1936) find evidence that the intravenous administration of saline may counteract the fall of blood during spinal anaesthesia.

There has been some discussion of the possibility that muscular relaxation with post-arteriolar dilatation may be concerned in the blood pressure fall during spinal anaesthesia. Sarnoff and Arrowood (1946) succeeded in producing "differential spinal block" with low concentrations of procaine which affected autonomic nerves but left the motor roots unaffected. The blood pressure fell to the same extent as in regular spinal anaesthesia and the conclusion was drawn that muscular flaccidity was not responsible for the blood pressure fall. Milwidsky and de Vries (1948) find no correlation between blood pressure fall and intramuscular pressure and agree with this conclusion. Koster (1942) and Lewis and Palser (1938) reach a similar conclusion.

## Use of Controlled Hypotension in Hypertensive Patients

Most hypertensive patients do not appear to suffer any lasting ill effects from a period of one or two hours of moderate hypotension with systolic blood pressures in the region of 70 or 80 mm. Hg, but cases of cardiac infarction have been described which seem to have been due to excessive blood pressure reduction. In some hypertensive patients blood pressure reduction leads to hemiparesis which, so far, in our experience of several patients, has always recovered when the blood pressure was restored to a higher level. It seems, however, that it is usually unwise to recommend the use of controlled hypotension during anaesthesia in a hypertensive patient because, during anaesthesia, symptoms indicative of serious impairment of the cerebral or coronary circulation are no longer available as an indication of the need to re-elevate the blood pressure. Neurosurgical operations may constitute an important exception to this rule because the operation may be greatly assisted by reduction of bleeding, and the method of Saunders (1952) and James, Coulter and Saunders (1953) may be used In this method comparatively small doses of ganglion blocking drugs are employed and the blood pressure is lowered by the application of suction to the legs. The level of the blood pressure can be lowered further or raised by increasing or decreasing the suction on the legs. In the absence of leg suction the blood pressure usually rises again promptly. (See also page 574).

# APPENDIX 4

## CLINICAL RECORD FORM

The figures 0, 1, 2, 3 signify "absent, slight, substantial, severe". Detail is entered in the spaces provided later.

### N. Z. MEDICAL RESEARCH COUNCIL

NAME: Age: Date:

---

### Present History of Hypertensive Symptoms

| | | *Severity* | *Duration* |
|---|---|---|---|
| 1 | Headache | 0 1 2 3 | |
| 2 | Dyspnoea at rest | 0 1 2 3 | |
| 3 | Dyspnoea on exertion | 0 1 2 3 | |
| 4 | Angina | 0 1 2 3 | |
| 5 | Other chest pain | 0 1 2 3 | |
| 6 | Black-outs | 0 1 2 3 | |
| 7 | Giddiness | 0 1 2 3 | |
| 8 | Palpitation | 0 1 2 3 | |
| 9 | Weakness & loss of energy | 0 1 2 3 | |
| 10 | Insomnia | 0 1 2 3 | |
| 11 | Tense or irritable temperament | 0 1 2 3 | |
| 12 | Menorrhagia | 0 1 2 3 | |
| 13 | Epistaxis | 0 1 2 3 | |
| 14 | Tinnitus | 0 1 2 3 | |

### Past History of Hypertensive Complications

1 Minor cerebral accidents NO YES If present, how many accidents?
  Encephalopathic
  Thrombotic
  Haemorrhagic (? Blood C S F.)

2 Major cerebral accidents NO YES If present, how many accidents?
  Thrombotic
  Haemorrhagic (? Blood C S F.)

3 Congestive heart failure NO YES

4 Cardiac asthma NO YES

5 Cardiac infarction NO YES

6 Angina NO YES Under consideration

7 Any other hypertensive complication NO YES

### Past History Aetiological

1 Pregnancies toxaemia NO YES Under consideration

2 Urinary tract disorders NO YES Under consideration
  (a) Nephritis
  (b) Pyelonephritis
  (c) Hydronephrosis
  (d) Calculus
  (e) Prostatic hypertrophy
  (f) Other renal disorders

3 Scarlet fever NO YES

4 Endocrine disturbances NO YES Under consideration
  (a) Menopause
  (b) Cortical hyperadrenia
  (c) Medullary hyperadrenia
  (d) Other endocrine disorders

5 HAUGEN, F. P. Hypertension: Management of the anesthesia period. Curr. Res. Anesth., 22: 152, 1943.
6 HILL, E. F. Blood-pressure during spinal anaesthesia. Brit. J. Surg, 24: 446, 1937.
7 JAMES, A., COULTER, R. L., and SAUNDERS, J. W. Controlled hypotension in neurosurgery with special reference to hypotension induced by pneumatic suction applied to the legs. Lancet, 1: 412, 1953
8 KENNEDY, W. P. The blood pressure in avertin anaesthesia. Brit. J. Anaesth., 8: 52, 1930.
9 KOSTER, H. Blood pressure changes during spinal anesthesia in non-operative cases. Arch. Surg. (Chicago), 45: 596, 1942.
10 LEWIS, D L., and PALSER, E. G. M. Changes in blood pressure and respiratory volume following a spinal anaesthetic. Brit. med. J., 1: 1202, 1938.
11 MILWIDSKY, H., and DE VRIES, A. Regulation of blood pressure during spinal anesthesia; observations on intramuscular pressure and skin temperature. Anesthesiology, 9: 258, 1948.
12 SARNOFF, S. J., and ARROWOOD, J G. Differential spinal block: A preliminary report Surgery, 20: 150, 1946.
13 SAUNDERS, J. W. Negative-pressure device for controlled hypotension during surgical operations Lancet, 1: 1286, 1952.
14 TAYLOR, G W., and LUND, C. C Blood pressure fall occurring in avertin anesthesia New Engl J. Med., 206. 612, 1932
15 WALKER, J. B Intravenous injection of hypertonic sodium chloride solution in the treatment of some conditions of low blood-pressure Brit. J. Surg, 24: 105, 1936
16 WHITACRE, R J, and SANKEY, B B Hypertension: Complications and choice of anesthesia Curr Res Anesth, 22. 99, 1943.
17 WRIGHT, S, and THOMPSON, J H. Effects of pure nitrous oxide anesthesia on human blood pressure. J Pharmacol, 38: 247, 1930

NAME:

**Detail of Past History-Aetiological**

**History not Closely or Directly Related to Arterial Hypertension**

NAME:

**Family History**

| | | | | |
|---|---|---|---|---|
| Mother | Alive | Dead | (Age of death | Cause of death |
| Father | Alive | Dead | (Age of death | Cause of death |
| Brothers | | | | |
| Sisters | | | | |
| Children | | | | |

**Detail of Present History**

**Detail of Past History Relating to Complications of Hypertension**

NAME:

Physical Examination (Supplementary Remarks)

NAME:

**Physical Examination** (Separate sheet for detail if required)

**General Remarks**

*Heart* (on clinical evidence)

| | | |
|---|---|---|
| Venous congestion | NO | YES |
| Enlarged or hypertrophied | NO | YES |
| Other abnormalities | NO | YES |
| Casual B.P. | Basal B.P. | |

*Lungs* — Abnormalities NO YES

*Abdomen* — Abnormalities NO YES

*C.N.S.* — Abnormalities NO YES

| | | | | | |
|---|---|---|---|---|---|
| *Retinae:* | Papilloedema | R eye | 0 1 2 3 ? | L eye | 0 1 2 3 ? |
| | Retinal oedema | R eye | 0 1 2 3 ? | L eye | 0 1 2 3 ? |
| (With | Haemorrhages | R eye | 0 1 2 3 | L eye | 0 1 2 3 |
| pupils | Soft exudates | R eye | 0 1 2 3 | L eye | 0 1 2 3 |
| dilated) | Hard exudates | R eye | 0 1 2 3 | L eye | 0 1 2 3 |
| | Vessels | R eye | 0 1 2 3 | L eye | 0 1 2 3 |

| | | | | |
|---|---|---|---|---|
| *Urine* | Albumen | 0 1 2 3 | Sugar | 0 1 2 3 |
| | Deposit | | | |

**Preliminary Note on Personality**

| | | | |
|---|---|---|---|
| Normal and stable | 0 1 2 3 | Morose | 0 1 2 3 |
| Nervous or tense | 0 1 2 3 | Depressed | 0 1 2 3 |
| Introspective | 0 1 2 3 | Hot tempered | 0 1 2 3 (Ask about this) |
| Neurotic | 0 1 2 3 | Aggressive | 0 1 2 3 |
| Worried | 0 1 2 3 | | |

# APPENDIX 6

## CLINIC ORGANIZATION

The specialized nature of the treatment of hypertension and the large number of patients involved makes it desirable to develop specialist clinics at least in large hospital centres. Many procedures found necessary in the case of hypertensive patients can be performed by trained technicians whose services not only aid administration of the clinic but by relieving the medical personnel of some routine tasks, make it possible to care efficiently for a large number of patients.

At the present time one of the most important contributions to the construction of a [illegible] patient is that, [illegible] time thereafter, [illegible] day, in the standing and sitting postures, notes being made of any symptoms in relationship to the blood pressure level at the time. Such relevant considerations as the effects of meals, long periods of standing, physical activity, etc., can be studied deliberately and the patient's régime adjusted accordingly

In our clinic we do not rely on just a few such tests but as many as 10 to 20 all-day tests are made, and many more in difficult cases. The measurement of blood pressure is entrusted to technicians who also draw the physicians' attention to any symptoms which occur. One technician can manage between 5 and 8 patients, depending on the amount of detailed information required.

Our own organization comprises a weekly outpatient session attended by 40 to 55 patients, and conducted by four physicians. We find that many patients who are on a combination of a Rauwolfia alkaloid

[illegible]

provide a sufficient indication.

For the most part the drugs are administered before or after breakfast, at about 2 p.m., and at bed time With long-acting drugs the pressure before the morning dose of drugs gives an indication of whether the night dose has been adequate. Where possible we like the morning pressure (before the morning dose is taken) to be under 180/110. All-day tests will give an indication of the proper dosage at bed time and 2 p m.

The régimes of by far the greatest number of patients are stabilized on an outpatient basis, the patients remaining at the clinic between 9 a.m. and 5 p m. each week day for a period of 2 to 3 weeks. The only

## APPENDIX 5

## TECHNIQUE FOR DETERMINING THE BASAL BLOOD PRESSURE IN GENERAL PRACTICE

Very satisfactory basal blood pressures can be obtained outside hospital as follows:

(1) The patient is informed that under special conditions of rest the blood pressure falls; that the lowest blood pressure obtained under such conditions provides useful information and may help to decide about the kind of treatment required. The patient is reassured that the test is not a prelude to any special or disturbing type of investigation and that all it is intended to do is to measure the blood pressure repeatedly for 15 minutes to discover the lowest reading. The essence of all this is that the patient must be relaxed and unconcerned.

(2) The patient is asked to abstain from food and drink from 9 p.m. on the night before the test is to be performed until the test is complete. A sedative suitable for the patient is administered at bed-time — say 1½ gr. pentobarbital, or even 3 gr. If the patient is unrelaxed next morning a further dose of 1½ gr. may be given.

(3) On the morning of the test the patient is asked to remain lying quietly in bed until the doctor arrives (preferably before 9 a.m.), unless it is necessary to empty the bladder or bowels. The doctor enters quietly, does not converse beyond encouraging the patient to relax mentally and physically. The blood pressure is measured regularly and with deliberate monotony every 30 seconds for 15 minutes, recording the results. The average of the two lowest readings is the basal pressure.

Some understanding of the patient is required if a true basal blood pressure is to be obtained. For example, if a business man has his eyes on the clock, with the intention of just managing to keep an appointment, it is most unlikely that the blood pressure will be basal. The arrangement to have a "general check over" after taking the pressure may cause enough tenseness to raise the blood pressure above the basal level.

# APPENDIX 6

## CLINIC ORGANIZATION

f the treatment of hypertension and the

necessary in the case of hypertensive patients ... trained technicians whose services not only aid administration of the clinic but by relieving the medical personnel of some routine tasks, make it possible to care efficiently for a large number of patients.

At the present time one of the most important contributions to the construction of a comfortable and efficient hypotensive régime for a patient is that, during the initiation of treatment and from time to time thereafter, the blood pressure should be followed throughout the day, in the standing and sitting postures, notes being made of any symptoms in relationship to the blood pressure level at the time. Such relevant considerations as the effects of meals, long periods of standing, physical activity, etc , can be studied deliberately and the patient's régime adjusted accordingly.

In our clinic we do not rely on just a few such tests but as many as 10 to 20 all-day tests are made, and many more in difficult cases. The measurement of blood pressure is entrusted to technicians who also draw the physicians' attention to any symptoms which occur. One technician can manage between 5 and 8 patients, depending on the

that many patients who are on a combination of a Rauwolfia alkaloid and a ganglion blocking drug have casual blood pressures in the standing posture at the outpatient clinic which range between 120 and 160 systolic, 80 and 100 diastolic Such results usually indicate that the morning dose has achieved a satisfactory control over the blood pressure level. All-day tests are used when routine clinic pressures do not provide a sufficient indication.

For the most part the drugs are administered before or after break-

pressure (before the morning dose is taken) to be under 180/110. All-day tests will give an indication of the proper dosage at bed time and 2 p m

The régimes of by far the greatest number of patients are stabilized on an outpatient basis, the patients remaining at the clinic between 9 a m. and 5 p m. each week day for a period of 2 to 3 weeks. The only

patients who are admitted to hospital for stabilization are those with congestive heart failure or who are recovering from strokes or in other ways are unsuitable for outpatient visits.

As far as is practicable, we arrange for grade 3 or grade 4 patients to attend monthly, though, when the blood pressure is very well controlled, the period is sometimes extended to 6 weeks. Other patients attend between monthly and 2-monthly, except when they come from a considerable distance when 3 or 6-monthly visits have to be accepted. We have the impression that maintenance of a good control over the blood pressure level is achieved by frequent visits of short duration rather than by infrequent visits at which more detailed studies of the patients are made.

## APPENDIX 7

## LATE ADDITIONS

**Appendix incorporating articles which had been overlooked or which became available late in 1956 or in 1957 during the printing of this volume.**

Chapter I None.

Chapter II Holland and Young (1956) using a 2.5 cm. cuff found the mean systolic pressure rose from 69 mm. Hg at birth to 99 mm. Hg at 6 months. There was no important difference between the *blood pressures of babies* born of toxaemic mothers as compared with the babies of normal mothers.

Sapp, Arney and Mattingly (1955) have compared the arterial *blood pressure in the upper and lower extremities* of adults. Using 12 cm. cuffs in each case, the mean blood pressures are 124/74 and 157/94. When an 18 cm. cuff is used on the thigh the pressure measured in the lower limb falls to 134/80.

Holland, W. W., and Young, I. M. Neonatal blood pressure in relation to maturity, mode of delivery, and condition at birth. Brit. med. J., 2: 1331, 1956.

Sapp, O. L., Arney, G. K., and Mattingly, T. W. Determination of arterial blood pressure in the lower extremity. Use of an eighteen centimeter sphygmomanometer thigh cuff. J. Amer. med. Ass., 159: 1727, 1955.

Chapter III Uchigasaki (1955) made an *inheritance* study in 10,000 Japanese and found: 50 per cent of hypertension in descendants when hypertension was recorded in 2 parents, 40 per cent in descendants with hypertension in 1 parent, 35 per cent when 1 or more uncles or aunts had hypertension, 27 per cent if a grandparent had hypertension, and 22 per cent if none of the ancestors had hypertension.

Dr. Ismet Eryetishir informs me that hypertension and hypertensive heart disease is the third most important cause of cardiovascular disturbances in Turkey. Vural and Eryetishir (1955) collected 1670 cases

[illegible] and 387 of essential hypertension and hypertensive disease [illegible] cent). Among the hypertensive patients there were 48 per cent males, [illegible] Sixty per cent of the cases were above 50 [illegible] present in 5.2 per cent. According to Vural and Eryetishir [illegible], Eryetishir and Vural (unpublished), Frank (1951) and User (1950) hypertension was the second most common cause of heart failure.

ERYETISHIR, I., and VURAL, I. L. Turkiyede kardiovaskular hastaliklarin etyolojisi (Ankara). Unpublished.

FRANK, E. Esansiyel hypertansiyon bilgisinin bugunki durumu. Klinik ilmi (Istanbul), 1: 3 and 87, 1951.

UCHIGASAKI, S On The Heredity of Essential Hypertension. Tohoku J. exp. Med. 61: 245, 1955.

USER, T. Erzurum yukseklikliminde dolasim yetersizliginin etyolojik faktorleri. Hekimlikte yeni gorusler (Istanbul). 4 969, 1950

VURAL, I L., and ERYETISHIR, I A preliminary report on the etiological factors of cardiovascular disease in Turkey. Askeri sihhiye dergisi (Ankara). 95, 1955

CHAPTER IV None.

CHAPTER V Joske et al. (1956) made isotope studies of the *anaemia of chronic renal insufficiency*. Red cell production was studied using $^{59}Fe$ and was reduced. Red cell destruction, studied with $^{51}Cr$, was increased in some cases but normal in most patients.

Short (1956) has analysed the radiological changes in the *lung in left ventricular failure*. He emphasises:

(1) clouding of the hilar region,

(2) frequent occurrence of hydrothorax,

(3) interlobular lines are less frequent than in mitral stenosis.

Martorell (1956) in reference to *hypertensive ulceration of the lower limbs*, which he described first in 1945, states that the diagnosis is based on:

(1) considerable hypertension in arm and leg vessels,

(2) overactive pulsation in the legs,

(3) the ulcers being at the junction of the lower and middle thirds of the legs,

(4) the ulcers being either bilateral or with pigment on one side in place of ulceration.

JOSKE, R. A, MCALISTER, J M, and PRANKERD, T. A. J. Isotope investigations of red cell production and destruction in chronic renal disease. Clin Sci, 15: 511, 1956.

MARTORELL, M. F. Ulcères de jambe chez les hypertendus. Extract from Les troubles trophiques des membres inférieurs d'origine veineuse. Masson et Cie, Paris, 114, 1956.

SHORT, D. S. Radiology of the lung in left heart failure. Brit. Heart J., 18: 233, 1956.

CHAPTER VI Milne and Muehrcke (1956) list the six cases of *primary aldosteronism* published so far with confirmation of the presence of aldosterone-secreting tumours. One almost symptomless patient was diagnosed at the Hammersmith hopital on the basis of hypertension and electrocardiographic indications of potassium deficiency — subsequently confirmed biochemically. Garrod et al. (1956a, b) discussed the significance of the assay of aldosterone in human urine and blood. On the basis of the literature and their own investigations, they point out that aldosterone secretion does not appear to be subject to pituitary control but that it is largely subservient to the requirements of body fluid volume control — a decrease calling for additional aldosterone secretion.

Eales and Linder (1956) described in detail the case of a woman with *primary aldosteronism.* A tumour was removed from the left adrenal gland. Prior to the operation the patient's blood pressure was 180/105; after recovery from the operation it was 130/95.

Of great interest is the report of Renold et al. (1957) that *amphenone* not only inhibits the thyroid gland by a thiourea-like action but affects the adrenal cortex and causes a decrease of aldosterone secretion, and in larger doses a decreased excretion of 17-ketosteroids. The substance has been used in patients and leads to elimination of sodium. The substance may aid the diagnosis of defects due to aldosteronism.

. For further references on *irradiation – induced malignant hypertension* the papers by Luxton (1953), Russell (1953) and Levitt and Oram (1956) should be consulted and correspondence in the British Medical Journal, Luxton (1956) and Wilson and Ledingham (1956).

*Non-cerebral injuries.* Excellent accounts of the course and treatment of post traumatic renal insufficiency are to be found in the papers of Teschan et al. (1955) and Smith et al. (1955). Hypertension, sometimes of considerable magnitude, occurred in several patients during treatment with the artificial kidney.

Brod (1956a, b) discusses the diagnosis of *chronic pyelonephritis* and the frequent occurrence of hyptertension as a complication. The original papers should be consulted. Briefly, Brod emphasises the importance in diagnosis of

(1) disproportionate prevalence of leucocytes over erythrocytes in the quantitative Addis count.

(2) marked hyposthenuria or isosthenuria along with satisfactory glomerular filtration (clearance of "endogenous" creatinine). The phenomenon may be unilateral.

(3) polyuria is more striking than in chronic glomerulonephritis and the specific gravity [illegible] below 1012.

He mentions that [illegible]

gest a disease of the [illegible] the high incidence of malignant hypertension in pyelonephritic hypertensives.

[illegible] 154 cases of *primary* systemic

[illegible]

the cases. In 55.9 per cent the readings [illegible] there was hypertension. Renal lesions were usual in autopsy cases. [illegible] (1956) describe the occurrence of renal insufficiency

[illegible]

trogen retention. The authors, and others [illegible] incidence of hypertension is increased when amyloidosis is present. As several patients were elderly some of the associated hypertension may have been [illegible]

Cleland et al. [illegible] in the treatmen[illegible] refer to the persistence [illegible] experienced hands the operative mortality is now below 10 per cent.


Brod, J. Chronic pyelonephritis and hypertension. Third International Congress of Internal Medicine. *Acta med scand*, **154**, suppl 312, p 122, 1956a.

Brod, J. Chronic pyelonephritis. Lancet, **1**: 973, 1956b.

Cleland, W. P., Counihan, T. B., Goodwin, J. F., and Steiner, R. E. Coarctation of the Aorta. Brit. med. J., **2**: 379, 1956.

Eales, L., and Linder, G. C. Primary aldosteronism. Quart. J. Med., n.s. **25**: 539, 1956.

Garrod, O., Simpson, S. A., and Tait, J. F. The significance of the assay of aldosterone in human urine and blood. Proc. roy. Soc. Med., **49**: 885, 1956a.

Garrod, O., Simpson, S. A., and Tait, J. F. Some factors affecting aldosterone secretion. Proc. roy. Soc. Med., **49**: 888, 1956b.

Levitt, W. M., and Oram, S. Irradiation-induced malignant hypertension: cured by nephrectomy. Brit. med. J., **2**: 910, 1956.

Luxton, R. W. Radiation nephritis. Quart. J. Med., n.s. **22**: 215, 1953.

Luxton, R. W. Irradiation-induced malignant hypertension. Brit. med. J., **2**: 1176, 1956.

Milne, M. D., and Muehrcke, R. C. Primary aldosteronism. Proc. roy. Soc. Med. **49**: 883, 1956.

Renold, A. E., Crabbé, J., Hernando-Avendano, L., Nelson, D. H., Ross, E. J., Emerson, K. Jr., and Thorn, G. W. Inhibition of aldosterone secretion by amphenone in man. New Engl. J. Med., **256**: 16, 1957.

Rukavina, J. G., Block, W. D., Jackson, C. E., Falls, H. F., Carey, J. H., and Curtis, A. C. Primary systemic amyloidosis: a review and an experimental, genetic, and clinical study of 29 cases with particular emphasis on the familial form. Medicine, **35**: 239, 1956.

RUSSELL, H. Renal sclerosis, "post-radiation nephritis" following upon irradiation of the upper abdomen. Edinb. Med. J., 60: 474, 1953.

SMITH, L. H. Jr., POST, R. S., TESCHAN, P. E., ABERNATHY, R. S., DAVIS, J. H., GRAY, D. M., HOWARD, J. M., JOHNSON, K. E., KLOPP, E., MUNDY, R. L., O'MEARA, M. P., and RUSH, B. F., Jr., Post-traumatic renal insufficiency in military casualties. II. Management, use of an artificial kidney, prognosis. Amer. J. Med., 18: 187, 1955.

TESCHAN, P. E., POST, R. S., SMITH, L., H. Jr., ABERNATHY, R. S., DAVIS, J. H., GRAY, D. M., HOWARD, J. M., JOHNSON, K. E., KLOPP, E., MUNDY, R. L., O'MEARA, M. P., and RUSH, B. F., Jr., Post-traumatic renal insufficiency in military casualties. Amer. J. Med., 18: 172, 1955.

WILSON, C., and LEDINGHAM, J. M. Irradiation-induced malignant hypertension Brit. med. J., 2: 1236, 1956.

ZUCKERBROD, M., ROSENBERG, B., and KAYDEN, H. J. Renal insufficiency and hypertension associated with secondary amyloidosis. Amer. J. Med., 21: 227, 1956.

CHAPTER VII None.

CHAPTER VIII Freis et al. (1955) and Rose et al. (1955) have made *circulation studies in dogs with a mechanical left ventricle.* The mean blood pressure changes induced by stepwise increases and decreases of pump output led to greater pressure changes when the outputs were low. They found that after adrenaline and noradrenaline the systemic blood pressure rises were due mainly to increase of peripheral resistance. The circulatory system of the dog differs from the human in that, in the dog, adrenaline and noradrenaline have very similar effects upon the heart and peripheral resistance.

Diamond and Howe (1956) have obtained evidence that chemoreceptors are present in the aorta of the cat which discharge afferent impulses through the left aortic nerve. There is still some dispute, however, about whether these bodies have a chemoreceptor function.

Sharpey-Schafer (1956) reports that, in fully developed tabes dorsalis, there is interference with baroceptor reflexes due to interference with the afferent pathways. Stimuli starting in the brain evoked normal responses. The overshoot of the blood pressure following the Valsalva manoeuvre was abolished. Large cough transients which cause forearm dilatation in normal subjects failed to do so in tabetics.

Roddie et al. (1956) find that heating increases the oxygen saturation of venous blood drawn from superficial but not from deep veins. They conclude that there is no increase in the blood flow in deep veins on heating.

Edholm et al. (1956) report plethysmograph experiments before and after inducing occlusion of the skin circulation by iontophoresis of adrenaline. They find that when the body temperature is raised by heating the increase in forearm blood flow is confined to the skin and superficial tissues.

England and Johnston (1956) found evidence of a small decrease of

peripheral resistance in dependent lower limbs, an expression of dilatation of vessels in response to increased transmural pressure.

DIAMOND, J., and HOWE, A. Chemoreceptor activity in the aortic bodies of the ca[illegible] 1956
EDHOL[illegible]
ENGLAND, R. M., and JOHNSTON, J. G. McC. The effect [illegible] venous congestion on the circulation through the toes Clin. Sci., 15: 587, 1956
FREIS, E. D., BROIDA, H. P., HUFNAGEL, C. A., and ROSE, J. C. Effects of varying the output of a mechanical left ventricle on the circulation in the dog. Amer. J. Physiol., 182: 191, 1955
RODDIE, I. C., SHEPHERD, J. T., and WHELAN, R. F. Evidence from venous oxygen saturation measurements that the increase in forearm blood flow during body heating is confined to the skin. J. Physiol. (Lond.), 134: 444, 1956
ROSE, J. C., FREIS, E. D., HUFNAGEL, C. A., and MASSULLO, E. A. Effects of epinephrine and nor-epinephrine in dogs studied with a mechanical left ventricle. Demonstration of active vasoconstriction in the lesser circulation. Amer. J. Physiol., 182: 197, 1955
SHARPEY-SCHAFER, E. P. Circulatory reflexes in chronic disease of the afferent nervous system. J. Physiol. (Lond.), 134: 1, 1956

[illegible] observations on *vascular reactivity* in renal and [illegible]

renoprival hypertension. He emphasises the importance of [illegible]. [illegible] of interest in this connection that Swingle et al. (1954) found that [illegible]

magnesium ion was decreased in the aortas of rats with experimental hypertension induced by a figure-of-eight ligature on a sole remaining kidney.

Unilateral renal ischaemia does not cause prolonged hypertension in dogs but Kezdi (1955) has made the interesting observation that *permanent hypertension* may be induced in the dog *if unilateral renal ischaemia is combined with bilateral carotid sinus denervation*. The hypertension persists after recovery of carotid sinus function, but apparently the baroceptors now regulate to a higher level of the blood pressure.

Jimenez Diaz and Pleguezuelo (1955) consider that *pressor substances released from minute arteries and arterioles are* normally inactivated by the renal tubules. In renal ischaemia or after nephrectomy this inactivation does not take place and the blood pressure rises. He regards the cellular intimal thickenings in certain kidneys as evidence of the development of increased pressor glandular activity.

RUSSELL, H. Renal sclerosis, "post-radiation nephritis" following upon irradiation of the upper abdomen. Edinb. Med. J., *60:* *474*, *1953.*

SMITH, L. H. Jr., POST, R. S., TESHCAN, P. E., ABERNATHY, R. S., DAVIS, J. H., GRAY, D. M., HOWARD, J. M., JOHNSON, K. E., KLOPP, E., MUNDY, R. L., O'MEARA, M. P., and RUSH, B. F., Jr., Post-traumatic renal insufficiency in military casualties. II. Management, use of an artificial kidney, prognosis. Amer. J. Med., **18:** **187**, **1955.**

TESCHAN, P. E., POST, R. S., SMITH, L., H. Jr., ABERNATHY, R. S., DAVIS, J. H., GRAY, D. M., HOWARD, J. M., JOHNSON, K. E., KLOPP, E., MUNDY, R. L., O'MEARA, M. P., and RUSH, B. F., Jr., Post-traumatic renal insufficiency in military casualties. Amer. J. Med., **18:** **172**, **1955.**

WILSON, C., and LEDINGHAM, J. M. Irradiation-induced malignant hypertension. Brit. med. J., **2:** **1236**, **1956.**

ZUCKERBROD, M., ROSENBERG, B., and KAYDEN, H. J. Renal insufficiency and hypertension associated with secondary amyloidosis. Amer. J. Med., **21:** **227**, **1956.**

CHAPTER VII None.

CHAPTER VIII Freis et al. (1955) and Rose et al. (1955) have made *circulation studies in dogs with a mechanical left ventricle.* The mean blood pressure changes induced by stepwise increases and decreases of pump output led to greater pressure changes when the outputs were low. They found that after adrenaline and noradrenaline the systemic blood pressure rises were due mainly to increase of peripheral resistance. The circulatory system of the dog differs from the human in that, in the dog, adrenaline and noradrenaline have very similar effects upon the heart and peripheral resistance.

Diamond and Howe (1956) have obtained evidence that chemoreceptors are present in the aorta of the cat which discharge afferent impulses through the left aortic nerve. There is still some dispute, however, about whether these bodies have a chemoreceptor function.

Sharpey-Schafer (1956) reports that, in fully developed tabes dorsalis, there is interference with baroceptor reflexes due to interference with the afferent pathways. Stimuli starting in the brain evoked normal responses. The overshoot of the blood pressure following the Valsalva manoeuvre was abolished. Large cough transients which cause forearm dilatation in normal subjects failed to do so in tabetics.

Roddie et al. (1956) find that heating increases the oxygen saturation of venous blood drawn from superficial but not from deep veins. They conclude that there is no increase in the blood flow in deep veins on heating.

Edholm et al. (1956) report plethysmograph experiments before and after inducing occlusion of the skin circulation by iontophoresis of adrenaline. They find that when the body temperature is raised by heating the increase in forearm blood flow is confined to the skin and superficial tissues.

England and Johnston (1956) found evidence of a small decrease of

The results of treatment are not yet statistically significant but in the direction of showing protection against the recurrence of coronary attacks.

Ancel Keys et al. (1957) conducted a rigidly controlled diet experiment in which the diet was constant except for the feeding of 100 gm. daily of different fats, namely: corn oil, sunflower seed oil, sardine oil [illegible] level on butter fat was [illegible] 35.8 mg. higher than on [illegible] on sardine oil. Thus the changes are not related in a simple way to essential fatty acid content nor to the degree of unsaturation.

[illegible] di [illegible] il has [illegible]

Cottet et al. (1953) found significant decreases in the serum cholesterol of normal rats and of patients with hypercholesterolaemia on feeding the sodium salt of $\alpha$-phenylbutyric acid. Steinberg and Fredrickson (1956), however, found no significant effects on the serum cholesterol levels from $\alpha$-phenylbutyric acid. Prolonged feeding of $\Delta^4$-cholestenone to rats suppresses $C^{14}$ acetate incorporation into cholesterol and decreases serum cholesterol levels by as much as 44 per cent. The substance is highly toxic when given in 1 per cent concentration in the diet but at lower doses (0 1 per cent) the blood cholesterol level was decreased without manifest toxicity. Enormous hypertrophy occurred in the adrenal glands. The end product, dihydrocholesterol, needs close investigation.

Corcoran et al. (1956) find, as we have done, that atherosclerotic complications are now the commonest cause of death in severe hypertensive patients under hypotensive therapy. They noted, moreover, a decrease of all lipoprotein fractions in serum after treatment, mostly with ganglion blocking drugs. The possibility is mentioned that this might be related to diminished food intake

Corcoran, A C, Lewis, L A, Dustan, H P, and Page, I H. Atherosclerotic complications in hypertensive disease Ann N.Y Acad Sci., 64: 620, 1956.

Cottet, J, Redel, J, Krumm-Heller, C, and Tricaud, M. E Pouvoir hypocholestérolémiant du phényl-éthyl-acétate de sodium (22 TH) sur le rat. Bull Acad nat Méd (Paris), 137: 441, 1953, cited by Steinberg, D, and Fredrickson, D S Inhibitors of cholesterol biosynthesis and the problem of hypocholesterolemia Ann N Y Acad Sci, 64: 579, 1956.

Keys, A, Anderson, J T, and Grande, F "Essential" fatty acids, degree of unsaturation, and effect of corn (maize) oil on the serum-cholesterol level in man Lancet, 1 66, 1957

Lindholm, H Studies in normal adults for variation in serum lipids with sex, age, relative body-weight, and with body-build. Scand J. clin. Lab. Invest., 8, suppl 23, 1956

Saile, F Über den Einfluss der vegetarischen Ernährung auf den Blutdruck. Med. Klin 26 929, 1930

DÍAZ, C. J., and PLEUGEZUELO, M. M. The pressor gland in urologic hypertension. Bull. Inst. med. Res. Univ. Madr., 8: 1, 1955.

KEZDI, P. Function of the carotid sinus in experimental renal hypertension. Trans. Amer. Coll. Card., 5: 15, 1955.

MCQUEEN, E. G. Vascular reactivity in experimental renal and renoprival hypertension. Clin. Sci., 15: 523, 1956.

SWINGLE, W. W., MAXWELL, R., BEN, M., BAKER, C., LE BRIE, S. J., and EISLER, M. A comparative study of aldosterone and other adrenal steroids in adrenalectomized dogs. Endocrinology, 55: 813, 1954.

TOBIAN, L. Jr., and BINION, J. Artery wall electrolytes in renal and DCA hypertension. J. clin. Invest., 33: 1407, 1954.

CHAPTER X Dr. W. Raab kindly drew my attention to some of the early literature on atherosclerosis in relation to hypertension. It is of particular interest, Dr. Raab pointed out, that "Saile (1930) studied the blood pressure of 225 monks, about one half of whom used consistently a completely *vegetarian diet* (avoidance of meat, eggs, butter and milk) whereas the other half belonged to orders in which a *mixed diet* is customary. Both the average blood pressure and the incidence of hypertension were considerably lower in the first group. Pressure levels above 175 mm. were found only among monks of the non-vegetarian group although the number of older persons (over 50) was much smaller in that group..."

Dr. Caroline Bedell Thomas (1956) has published the results of a ten year survey of data obtained from medical students, including blood cholesterol levels. *Hypercholesterolaemia in young people* was linked with a family tendency to cardiovascular disease (especially of coronary artery disease in fathers) and diabetes. A definite association appears to have been established.

A study of the *relationship of serum lipids to age, relative body weight and body build* was made by Lindholm (1956). Persons with a family history of diseases known to be associated with changes in the serum lipids were excluded. The total lipids, phospho-lipids, total cholesterol and free cholesterol did not vary with body build or relative body weight; they increase with age in females and increase with age in males but only up to age 50.

Stamler et al. (1956) referred to the dispersal of atheromatous plaques in cockerels treated with oestrogens. When insulin is given it interferes with the *protective ability of the oestrogens*. Oestrogens increase plasma phospholipids and lower cholesterol (less regularly). In man 10 mg. per day has been given orally of equine oestrogens (Premarin). This dose consistently feminized and altered the serum lipid-lipoprotein pattern. Such changes were sufficiently consistent to be used as a sign of continued adherence to therapy. There was considerable decrease of libido and potency. Oestrogen-androgen combinations were ineffective for protection and feminization was not necessarily prevented.

Hatch (1954) notes that, following a period of sodium chloride re- ... followed by the appearance

... is that sodium may be retained in bone in association ... than chloride.

Dahl et al. (1955) report that during prolonged sodium restriction (6 mEq. Na per day) the electrolyte loss from the skin fell to 0.03 to 2.59 mEq. of sodium per day. The results obtained suggested the possibility that, under conditions of severe salt restriction, electrolyte might be reabsorbed from the skin.

DAHL, L. K., STALL, B. G., and COTZIAS, G. C. Metabolic effects of marked sodium restriction in hypertensive patients Skin electrolyte losses. J. clin. Invest, 34: 462, 1955.

HATCH, F. T. Effects of withdrawal and restoration of dietary sodium chloride upon urinary electrolytes in patients with hypertension. Metabolism, 3: 160, 1954

RENWICK, R., ROBSON, J S, and STEWART, C. P. Observations upon the withdrawal of sodium chloride from the diet in hypertensive and normotensive individuals. J clin. Invest, 34: 1037, 1955

... relief of angina was noted.

Currens et al. (1956) used *protoveratrine* in hypertensions of pregnancy. The dosage was 0 5—1 5 mg., 6—8 hourly, increasing the dose by 0 1—0.2 mg. per dose or per day until a satisfactory response was obtained. In these disorders they consider protoveratrine to be superior to pentolinium.

Calliauw (1955) has investigated the pressor responses to protoveratrine A which are revealed when the hypotensive action is abolished by denervation of the carotid sinuses and aortic regions. He considers the pressor response is due to central stimulation. It may be explained in part by release of adrenaline and noradrenaline. Secondary centres in the spinal cord are also stimulated.

Stroer (1956) described the hypotensive action of extracts of *Juglans Regia L.* (derived from an alcoholic extract of walnut leaves collected in July). The depressor activity is associated with vasodilatation and depressor reflexes appear to be stimulated.

Yim et al (1956) refer to the action of 1-phenyl-2-dimethylamino-ethoxy-methyl tetrazole hydrochloride (*TT*-209), which depresses cardiac and smooth muscle. There is some tachyphylaxis.

CALLIAUW, L On the hypertensive action of protoveratrine A. Arch. int. Pharmacodyn, 107: 75, 1956

CURRENS, J H., REID, D. E, and NEWELL, J. L. Hypertension associated with pregnancy. J. Amer. med. Ass, 161: 1232, 1956.

STAMLER, J., PICK, R., and KATZ, L. N. Experiences in assessing estrogen anti-atherogenesis in the chick, the rabbit, and man. Ann. N.Y. Acad. Sci., 64: 596, 1956.

STEINBERG, D., and FREDRICKSON, D. S. Inhibitors of cholesterol biosynthesis and the problem of hypercholesterolemia. Ann. N.Y. Acad. Sci., 64: 579, 1956.

THOMAS, C. B. Observations on some possible precursors of essential hypertension and coronary artery disease: V. Hypercholesteremia in healthy young adults. Amer. J. med. Sci., 232: 389, 1956.

CHAPTER XI Brandfonbrener et al. (1955) report a decrease in the cardiac output with age. As the mean blood pressure rises with age, it would appear that there is an even greater percentage increase of the mean increase of the peripheral resistance with age.

Fazekas et al. (1955) in studies of cerebral blood flow found decreases below the value in young normals occurred in elderly subjects without, however, significant change in cerebral oxygen utilization or in the functions of higher centres. Essential hypertension in young and old hypertensives led to increased cerebral vascular resistance. They had the impression that hypertension accelerates cerebral vascular disease.

BRANDFONBRENER, M., LANDOWNE, M., and SHOCK, N. W. Changes in cardiac output with age. Circulation (N.Y.), 12: 557, 1955

FAZEKAS, J. F., KLEH, J., and FINNERTY, F. A. Influence of age and vascular disease on cerebral hemodynamics and metabolism. Amer. J. Med., 18: 477, 1955

CHAPTER XII None.

CHAPTER XIII None.

CHAPTER XIV Wells (1956) refers to the reversal of eye ground changes following sympathectomy. He considers that relief of headache is not psychosomatic.

St. Clair and Barnett (1956) studied the foot blood flows in 8 subjects who had undergone lumbar sympathectomy 10 months to 20 years previously. Four of the 8 subjects had hyperaemia persisting 3 to 20 years.

ST. CLAIR, W. A., and BARNETT, A. J. The long term effect of lumbar sympathectomy on the foot blood flow. Alfred Hosp. clin. Rep. (Melbourne), 6: 85, 1956

WELLS, C. A. The surgery of hypertension: a five-year follow-up. Scot. Med. J., 1: 245, 1956.

CHAPTER XV Renwick et al. (1955) differ from Perera and Blood (1946) in that they observe no difference from the normal in the capacity of hypertensives to retain salt when subjected to withdrawal of sodium chloride from the diet. There was also a comparable loss of potassium in the two groups.

(1956a) that lysergic acid diethylamide, which has been described as an antimetabolite of 5-HT, may exhibit serotonin-like properties when acting upon the heart of the clam and of the dog, and is 1 to 3 times as active as 5-HT in raising [illegible]
ever, lysergic acid diethy[illegible]

In terms of current co[illegible] not be regarded as paradoxical. It is possible that substances chemically related to 5-HT may combine with receptors either to induce or to block serotonin-like actions. One and the same compound might be able to induce some serotonin-like actions yet block others. Moreover, in the dog, (Shaw and Woolley, 1956a) a serotonin "antimetabolite" BAS (1-benzyl-2,5-dimethyl-serotonin) antagonizes the pressor effect [illegible]

[illegible] action of serotonin.

Paasonen and Vogt (1956) found that sublethal doses of amphetamine reduced the 5-HT content of the dog hypothalamus by one-half though, of course, excitment resulted. This raises a difficulty in attempting to explain reserpine sedation in terms of 5-HT depletion.

The part played by 5-HT in the brain must be considered also in relation to the observation of Cerletti and Rothlin (1955) that BOL 148 (a derivative of lysergic acid) is a powerful antagonist to 5-HT, but does not cause the mental disturbances characteristic of lysergic acid diethylamide.

The observation of Shore, Silver and Brodie (1955) that reserpine and 5-HT potentiate the action of hexobarbitone in mice should probably not be used as strong evidence of a relationship between their central nervous actions (Salmoiraghi, Sollero and Page, 1956; Fastier, 1956).

My colleagues Fastier, Speden and Waal (1957) have shown that numerous other substances (e g. adrenaline, methoxamine, ergotamine, priscol, histamine) possess hypnotic-prolonging activity and that the prolonged sleeping time is influenced by fall in body temperature. When this is prevented the 5-HT no longer greatly prolongs the sleeping time of mice

Study of the relationship between 5-HT and mental activity is made more difficult by uncertainty as to whether effects are due to loss of 5-HT from nerve cells or increase in the concentration of 5-HT in the surrounding region due to its liberation. As Feldberg (1956) pointed out, the long-lasting action of reserpine is more consistent with the loss of 5-HT being the cause of central effects, if indeed they have anything to do with 5-HT.

The preparation at Argonne National Laboratory of radioactive reserpine (by growing the plant in an atmosphere containing radioac-

PÖLDRE, A. Two-year results of hydergine therapy in hypertension and other circulatory disturbances. Acta med. scand, 155: 437, 1956.
STROER, W. F. H. On the mechanism of the hypotensive action of the extract of Juglans Regia L. Acta physiol. pharmacol. neerl., 5: 23, 1956.
YIM, G. K. W., GROSS, E. G. and KEASLING, H. H. The hypotensive action of 1-phenyl-2-dimethylaminoethoxymethyl tetrazole hydrochloride (TT-209). J. Amer. pharm. Ass., 45: 664, 1956.

## CHAPTER XVII *Pharmacology of reserpine.*

Gillis and Lewis (1956) consider that reserpine may have a general non-specific depressant effect upon contractile tissue. Thus, the contractions of guinea pig ileum in response to acetylcholine, histamine acid phosphate, 5-HT, and barium chloride were all reduced in organ bath experiments by reserpine (5 to 30 $\mu$g. in a 2 ml. bath). Somewhat similar effects were demonstrable on preparations such as the frog rectus abdominis muscle, the perfused kitten heart, the rat uterus, and the spinal cat (for pressor responses to adrenaline).

Gross et al. (1955) treated renal hypertensive rats with reserpine. Blood pressure falls were maintained while the drug was administered but the blood pressures rose again when the drug was withdrawn.

In experiments on rhesus monkeys Weiskrantz and Wilson (1956) obtained evidence that reserpine depressed, temporarily, both performance and learning.

A substantial contribution to the pharmacognosy, chemistry and pharmacology has been published by Woodson, Youngken, Schlittler and Schneider (1957). An excellent account is given of some of the less well known alkaloids.

*Relationship between reserpine and serotonin (5-hydroxytryptamine, 5-HT).*

While evidence has accumulated that reserpine has sites of action outside the central nervous system, within the central nervous system more information concerning the relationship between reserpine and 5-HT metabolism has become available. The situation (April, 1957) is tremendously exciting but far from tidy.

Sheppard et al. (1955) have shown that there is no parallel between the content of reserpine in the brain and its duration of action. It has been shown, however, that reserpine releases 5-HT from the brain (Pletscher, Shore and Brodie, 1955; Paasonen and Vogt, 1956).

Hess, Shore and Brodie (1956) report that reserpine enters the brain readily after intravenous injection (15 min.) and rapidly disappears while the central nervous action becomes more pronounced. The effect on the central nervous system appears to be related more closely to the brain content of 5-HT than to the concentration of reserpine.

Possibly of interest in relation to the hypotensive action of reserpine, certainly interesting in relation to severe nervous side effects (depression, peculiar dreams, etc.), is the observation of Shaw and Woolley

ing upon the heart of the clam and of the dog, and is ... as active as 5-HT in raising the blood pressure of dogs. In the brain, however, lysergic acid diethylamide appears to act in opposition to 5-HT.

In terms of current concepts of pharmacodynamics such results need not be regarded as paradoxical. It is possible that substances chemically related to 5-HT may combine with receptors either to induce or to block serotonin-like actions. One and the same compound might be able to induce some serotonin-like actions yet block others. Moreover, in the dog, (Shaw and Woolley, 1956a) a serotonin "antimetabolite" BAS (1-benzyl-2,5,dimethyl-serotonin) antagonizes the pressor effect not only of serotonin but also of lysergic acid diethylamide. Another anti-metabolite of serotonin, BAB (Benzyldimethylbufotenin) described by Shaw and Wooley (1956b) also protects dogs against the pressor action of serotonin.

Paasonen and Vogt (1956) found that sublethal doses of amphetamine reduced the 5-HT content of the dog hypothalamus by one-half though, of course, excitment resulted. This raises a difficulty in attempting to explain reserpine sedation in terms of 5-HT depletion.

The part played by 5-HT in the brain must be considered also in relation to the observation of Cerletti and Rothlin (1955) that BOL 148 (a derivative of lysergic acid) is a powerful antagonist to 5-HT, but does not cause the mental disturbances characteristic of lysergic acid diethylamide.

The observation of Shore, Silver and Brodie (1955) that reserpine and 5-HT potentiate the action of hexobarbitone in mice should robably not be used as strong evidence of a relationship between their entral nervous actions (Salmoiraghi, Sollero and Page, 1956; Fastier, 956).

My colleagues Fastier, Speden and Waal (1957) have shown that numerous other substances (e g adrenaline, methoxamine, ergotamine, priscol, histamine) possess hypnotic-prolonging activity and that the prolonged sleeping time is influenced by fall in body temperature. When this is prevented the 5-HT no longer greatly prolongs the sleeping time of mice

Study of the relationship between 5-HT and mental activity is made more difficult by uncertainty as to whether effects are due to loss of 5-HT from nerve cells or increase in the concentration of 5-HT in the surrounding region due to its liberation. As Feldberg (1956) pointed out, the long-lasting action of reserpine is more consistent with the loss of 5-HT being the cause of central effects, if indeed they have anything to do with 5-HT.

The preparation at Argonne National Laboratory of radioactive reserpine (by growing the plant in an atmosphere containing radioac-

tive carbon dioxide) may solve some of the outstanding problems.

Woolley and Shaw (1956) raised the question of whether essential hypertension might be due to 5-HT and Wilkins and Hollander (1956a) found that BAS caused a mild fall of blood pressure in about one third of hypertensive patients. It had reserpine-like side effects such as sedation, increased intestinal mobility, nasal congestion and bradycardia. However, in a preliminary clinical trial, the anti-serotonin BAB, administered orally, did not appear to have a significant hypotensive effect (Wilkins and Hollander, 1956b). Indeed it seems unlikely that 5-HT is concerned fundamentally in the pathogenesis of essential hypertension. Hypertension is not a symptom of "carcinoidosis" in which large amounts of 5-HT are liberated from argentaffin tissue.

Erspamer et al. (1956) treated rats chronically with 5-HT without causing any lasting blood pressure increase, though necrotic cortical renal lesions developed.

## Clinical Reports

Reports published late in 1956 or early in 1957 on the use of Rauwolfia alkaloids for hypertension and for mental disorders are mainly confirmatory of earlier writings.

Lewis et al. (1956) found clinical improvement of angina occurred in a considerable majority of anginal patients on the alseroxylon fraction of R. Serpentina.

Harris (1956) used 0.5 mg. reserpine one to three times daily in 34 elderly hypertensive patients, average 70.3 years of age. The average blood pressure fell from 189/100 to 173/88.

Achor and Hanson (1956) compared whole root preparations of R. Canescens and R. Serpentina in respect of their effects on the blood pressure and the side effects. They found no special difference and encountered depressive reactions with both. (But we find the pure alkaloids reserpine and canescine differ significantly).

Gibbons et al. (1956) stressed the importance of serious mental illness following reserpine administration. They had 4 examples among 58 patients. Their dose was up to 1.5 mg. per day They found as we have done that the mental illness may linger on long after withdrawal of the reserpine.

Hodgkinson (1956) used 1—2 mg. daily of reserpine for 12—18 months. He encountered one severe depression in 34 patients.

In an editorial of the Canadian Medical Association Journal the recommended maintenance dose of reserpine is 0.25 mg. daily for the treatment of hypertension and 2.0 mg. daily for the treatment of psychotic illnesses. During the last 2 years we have, with rare exceptions, restricted the dose of reserpine to 0.5 mg. daily. This precaution has not eliminated the side effect of mental depression but serious

mental depression has not occurred and the response to reduction of the dose or withdrawal of the drug has been prompt.

Birchall et al. (1956) have compared the various well known hypotensive drugs. They have abandoned hydralazine and veratrum and prefer Rauwolfia alkaloids, pentolinium and chlorisondamine.

Diminished enthusiasm for the treatment of psychotic and psychoneurotic illness by Rauwolfia alkaloids has followed the realization that patients may be made worse. McGrath and Ryan (1956) report the occurrence of reserpine depression in psychotic patients. Moore and Martin (1957) describe severe depression with suicidal preoccupation in schizo-affective psychotic patients. They confirm our view that a past history of endogenous depression is a contraindication to the use of the drug. Nevertheless, Moore and Martin feel that many patients, especially acute schizophrenics, improve; chronic schizophrenics are not helped so much. Penman and Dredge (1956) and Pearl et al. (1956) also find the drug unhelpful in chronic regressed schizophrenics; and Shepherd and Watt (1956) express a preference for chlorpromazine.

An account of other tranquillizing drugs such as chlorpromazine and azacyclonol (Frequel) is outside the scope of this volume, but their relation to reserpine is discussed in a valuable paper by Himwich (1955).


ACHOR, R. W P, and HANSON, N O Hypertension treated with Rauwolfia *canescens* A comparison with Rauwolfia serpentina New Engl. J. Med, 255· 646, 1956

BIRCHALL, R, WEBER, G F, and BATSON, H M The chemotherapy of hypertension Amer Practit (Philad), 7 1104, 1956.

CERLETTI, A, and ROTHLIN E Role of 5-hydroxytryptamine in mental diseases and its antagonism to lysergic acid derivatives Nature, (Lond). 176: 785, 1955

[illegible] 956.

[illegible] ynamic and [illegible] rats treated [illegible] with the substance Arch int Pharmacodyn, Gand. 106: 122, 1956

FASTIER, F N Prolongation of hypnosis by 5-hydroxytryptamine (serotonin). [illegible]

[illegible] Prolongation of chloral hydrate [illegible] (serotonin) and by certain other drugs, *in press*. Brit J Pharmacol, 1957

FELDBERG, W *Hypotensive drugs* Edited Harington, M Pergamon Press, London and New York, 1956, p. 68

GIBBONS, J E, MULLER, J C, PRYOR, W W, and ORGAIN, E. S. Newer drugs in the treatment of hypertension J Amer med Ass, 162: 92, 1956.

GILLIS, C N, and LEWIS, J. J A note on the pharmacology of reserpine. J. Pharm Pharmacol, 8 608, 1956a

GILLIS, C N, and LEWIS, J. J Antagonists of the action of reserpine on smooth muscle Nature, (Lond), 178 859, 1956b

GROSS, F, NOELPP, B, SULSER, F, DOEBELIN, R., and KÜNDIG, H. Vergleichende Untersuchungen uber die medikamentöse Beeinflussung verschie-

dener Formen von experimenteller Hypertension. Klin. Wschr., **15/16:** 372, 1955.
HARRIS, R. Reserpine therapy in hypertension. J. Amer. Geriat. Soc., **4:** 269, 1956.
HESS, S. M., SHORE, P. A., and BRODIE, B. B. Persistance of reserpine action after the disappearance of drug from brain: effect on serotonin. J. Pharmacol., **118:** 84, 1956.
HIMWICH, H. E. Prospects in psychopharmacology. J. nerv. ment. Dis, **122:** 413, 1955.
HODGKINSON, R. The effects of reserpine on hypertensive patients over a period of two years. Brit. Heart J., **18:** 523, 1956
LEWIS, B. I., LUBIN, R. I., JANUARY, L. E., and WILD, J.B. *Rauwolfia serpentina* in the treatment of angina pectoris. Circulation (N.Y.), **14:** 227, 1956.
LEWIS, J J. The Rauwolfia alkaloids J. Pharm. Pharmacol., *8:* 465, 1956.
MCGRATH, S. D., RYAN, J. P. A., and FENNELLY, J. J The use of reserpine ("Serpasil") in psychiatry. J. Irish med. Ass., *39: 1, 1956.*
MOORE, J. N. P., and MARTIN, E. A. Trial of reserpine in treatment of schizophrenia [illegible]
PAASONEN, [illegible] ubstance P and [illegible] J. Physiol. (Lond.), **131:** 617, 1956
PEARL, D., VANDER KAMP, H., OLSEN, A. L, GREENBERG, P. D, and ARMITAGE, S G The effects of reserpine on schizophrenic patients. Arch. Neurol. Psychiat (Chicago), **76:** 198, 1956.
PENMAN, A S, and DREDGE, T E. Effect of reserpine and open-ward privileges on chronic schizophrenics Arch Neurol Psychiat. (Chicago), **76:** 42, 1956
PLETSCHER, A, SHORE, P A., and BRODIE, B. B. Serotonin release as a possible mechanism of reserpine action Science, **122**· 374, 1955
SALMOIRAGHI, G C, SOLLERO, L, and PAGE, I H Blockade by bromlysergic-acid-diethylamide (BOC) of [illegible] serpine on hexobarbital hyp[illegible]
SHAW, E, and WOOLLEY, D W. [illegible] diethylamide Science, **124:** 121, 1956a
SHAW, E, and WOOLLEY, D W Benzyldimethylbufotenin, a powerful anti-metabolite of serotonin Proc. Soc exper Biol (N Y), **93:** 217, 1956b.
SHEPHERD, M, and WATT, D C A controlled clinical study of chlorpromazine and reserpine in chronic schizophrenia J Neurol. Neurosurg Psychiat, **19** 232, 1956
SHEPPARD, H, LUCAS, R C, and TSIEN, W H. The metabolism of reserpine $C^{14}$. Arch. int Pharmacodyn, **103**. 256, 1955.
SHORE, P. A, SILVER, S L, and BRODIE, B B Interaction of reserpine, serotonin and lysergic acid diethylamide in brain. Science, **122:** 284, 1955.
WEISKRANTZ, L, and WILSON, W A, Jr Effect of reserpine on learning and performance Science, **123:** 1116, 1956.
WILKINS, R. W., and HOLLANDER, W Serotonin, antisertonins and hypertension. Circulation (N Y), **14** 1018, 1956a
WILKINS, R. W., and HOLLANDER, W Cited by Shaw, E, and Woolley, D W. Benzyldimethylbufotenin, a powerful anti-metabolite of serotonin (22712). Proc Soc. exper. Biol (N Y), **93**· 217, 1956b.
WOODSON, R E, Jr., YOUNKEN, H W, SCHLITTLER, E. and SCHNEIDER, J. A. Rauwolfia; Botany, Pharmacognosy, Chemistry and Pharmacology. Little, Brown and Co. (Canada) Ltd, 1957
WOOLLEY, D. W. and SHAW, E N. Antiserotonins in hypertension and the anti-metabolite approach to chemotherapy. Science, **124**. 34, 1956.

(1958) found that, in general, the

was similar to their potency in man.

action of hexamethonium in mice.

choline and hypoxia were reduced by injections of methonium. Dontas and Nickerson (1956) also find that penta- and hexamethonium block the chemoreceptor response to lobeline and acetylcholine and prolong the response to hypoxia. However, in the course of their experiments the surprising observation was made that ganglion blocking agents would stimulate chemoreceptors.

BLACKMAN, J. G., FASTIER, F. N., PATEL, C. M. and WONG, L. C. K. Assessment of depressor activity and mydriatic activity of hexamethonium analogues Brit. J. Pharmacol 11: 282, 1956

DONTAS, A. S. and NICKERSON, M. Effects of stimulants and of ganglionic blocking agents on carotid chemoreceptors Arch. int. Pharmacodyn., 106: 312, 1956.

GOLLWITZER-MEIER, K. and WITZLEB, E. Zur Wirkung bisquaternärer Ammoniumsalze auf das Glomus caroticum der Katze Pflüg. Arch. ges. Physiol., 256: 381, 1953

CHAPTER XIX The advent of mecamylamine has shown that still more interesting ganglion blocking drugs may become available, for this substance has opened up a new chemical group.

Freis and Wilson (1956a) confirm their previous finding that drug toleration is slight or non-existent with mecamylamine. In 30 severe cases the average daily dose was 29 mg. In 21 severe cases our average daily dose was 35 mg.

Doyle et al. (1956) have reported their experience with mecamylamine in 45 hypertensive patients. Five patients discontinued treatment within a month of starting because of side effects and four of these were more comfortable on parenteral pentolinium. In general, control over the blood pressure was better with oral mecamylamine than with parenteral pentolinium but side effects were often more pronounced, especially the gastro-intestinal symptoms. Persistent vomiting or nausea occurred in six patients which is a much higher incidence of this symptom than is encountered with pentolinium. A majority of their patients preferred mecamylamine. Little or no drug toleration was observed.

chlorisondamine. The effective oral dose of mecamylamine was only slightly greater than the subcutaneous dose. Mecamylamine was abandoned in 13 patients; it was the ganglion blocking agent of choice in 22 patients.

dener Formen von experimenteller Hypertension. Klin. Wschr., **15/16**: 372, 1955.

Harris, R. Reserpine therapy in hypertension. J. Amer. Geriat. Soc., **4**: 269, 1956.

Hess, S. M., Shore, P. A., and Brodie, B. B. Persistance of reserpine action after the disappearance of drug from brain: effect on serotonin. J. Pharmacol., **118**. 84, 1956.

Himwich, H. E. Prospects in psychopharmacology. J. nerv. ment. Dis, **122**: 413, 1955

Hodgkinson, R. The effects of reserpine on hypertensive patients over a period of two years. Brit. Heart J., **18**: 523, 1956.

Lewis, B. I., Lubin, R. I., January, L. E., and Wild, J. B. *Rauwolfia serpentina* in the treatment of angina pectoris. Circulation (N.Y.), **14**: 227, 1956.

Lewis, J. J. The Rauwolfia alkaloids. J Pharm Pharmacol., **8**: 465, 1956.

McGrath, S D, Ryan, J. P. A., and Fennelly, J. J. The use of reserpine ("Serpasil") in psychiatry. J. Irish med. Ass., **39**: 1, 1956

Moore, J. N. P., and Martin, E A. Trial of reserpine in treatment of schizophrenia. Brit med J., **1**: 8, 1957.

Paasonen, M. K., and Vogt, M. The effect of drugs on the amounts of substance P and 5-hydroxytryptamine in mammalian brain J. Physiol. (Lond), **131**: 617 1956

Pearl, D, [illegible] P. D., and Armitage, S. G [illegible] patients Arch. Neurol. Psychiat (Chicago), **76**: 198, 1956.

Penman, A S, and Dredge, T. E Effect of reserpine and open-ward privileges on chronic schizophrenics Arch Neurol Psychiat (Chicago), **76**: 42, 1956

Pletscher, A, Shore, P A, and Brodie, B. B Serotonin release as a possible mechanism of reserpine action Science, **122** 374, 1955.

Salmoiraghi, G C, Sollero, L, and Page, I H Blockade by bromlysergic-acid-diethylamide (BOC) of the potentiating action of serotonin and reserpine on hexobarbital hypnosis J Pharmacol., **117**. 166, 1956.

Shaw, E, and Woolley, D W Some serotonin-like activities of lysergic acid diethylamide Science, **124** 121, 1956a.

Shaw, E, and Woolley, D. W Benzyldimethylbufotenin, a powerful anti-metabolite of serotonin Proc Soc exper Biol (N Y), **93** 217, 1956b

Shepherd, M, and Watt, D C A controlled clinical study of chlorpromazine and reserpine in chronic schizophrenia J Neurol Neurosurg Psychiat, **19**. 232, 1956

Sheppard, H, Lucas, R C, and Tsien, W H The metabolism of reserpine C[14]. Arch. int Pharmacodyn, **103** 256, 1955

Shore, P A, Silver, S L, and Brodie, B B Interaction of reserpine, serotonin and lysergic acid diethylamide in brain Science, **122**· 284, 1955.

Weiskrantz, L, and Wilson, W A, Jr. Effect of reserpine on learning and performance Science, **123** 1116, 1956.

Wilkins, R. W, and Hollander, W Serotonin, antisertonins and hypertension. Circulation (N Y), **14**· 1018, 1956a

Wilkins, R W., and Hollander, W Cited by Shaw, E, and Woolley, D. W Benzyldimethylbufotenin, a powerful anti-metabolite of serotonin (22712). Proc. Soc. exper Biol. (N Y), **93** 217, 1956b

Woodson, R E, Jr, Younken, H W, Schlittler, E and Schneider, J A. Rauwolfia; Botany, Pharmacognosy, Chemistry and Pharmacology. Little, Brown and Co (Canada) Ltd, 1957

Woolley, D. W. and Shaw, E. N. Antiserotonins in hypertension and the anti-metabolite approach to chemotherapy. Science, **124**· 34, 1956.

of subarachnoid haemorrhage with satisfactory results. We have *treated several* patients in this way usually with recovery, but, on occasion, recurrence of haemorrhage has taken place with fully normotensive levels of the blood pressure and *in the absence of straining*. Our impression also is that something may be gained by a hypotensive régime.

Graham and Maxwell (1956) *find that despite treatment with pen*tolinium and reserpine, of the patients in Groups III and IV 47 per cent of males died within an average of 19 months, and 35 per cent of [illegible] average of 23 months.

[illegible]

hand. They have also reported good results with mecamylamine.

Fishberg (1956) sums up his review "The treatment of Essential Hypertension" as follows: "At present, with all its grave shortcomings, *it appears that the combination of pentolinium and* Rauwolfia with salt restriction constitutes the most frequently helpful pharmacologic treatment of severe essential hypertension, including the cases in the *malignant phase.*"


ABRAHAMS, D G, and WILSON, C. Effect of hypotensive drugs on renal function in chronic renal disease Lancet, 1: 68, 1957

BROMAGE, P R. Hypotension and vital capacity. Anaesthesia, 11: 139, 1956.

DAVIGNON, A, LEMIEUX, G., and GENEST, J Ansolysen in the treatment of arterial hypertension Canad med. Ass J, 74: 802, 1956.

DOYLE, A E, MURPHY, E A, and NEILSON, G. H The hypotensive action of mecamylamine Brit med J, 2 1209, 1956

FREIS, E D, and WILSON, I M Mecamylamine, a new, *orally effective*, hypotensive agent Arch intern Med, 97. 551, 1956a.

FREIS, E D, and WILSON, I M Results of prolonged treatment with pentolinium tartrate with *special reference to the addition of* Rauwolfia, hydralazine or both Circulation (N Y), 13· 856, 1956b

FISHBERG, A M *The treatment of essential hypertension*. Med. Clin. N. Amer., 40· 1325, 1956

GRAHAM, J G, and MAXWELL, R D H. Hypertension. J. Amer. Geriat. Soc., 4 448, 1956

PARK, W W, and COCKERSOLE, F J *Hexamethonium lung: report of a case* associated with pregnancy J Obstet. Gynaec. Brit. Emp., 63: 728, 1956.

SCHROEDER, H A *The control of arterial* hypertension in older individuals. J Geront, 11 397, 1956

SLOSBERG, P S *Hypotensive* therapy in acute intracranial bleeding. J. Mt. Sinai Hosp, 23 825, 1956

SMIRK, F H, and MCQUEEN, E G *Use of* mecamylamine in the management of hypertension Brit med J. 1 422, 1957.

SMITH, T P *Acute hallucinatory* episode following hexamethonium bromide. Brit med J, 1 1088, 1956.

WILSON, C, and ABRAHAMS, D. G The treatment of hypertension in primary renal disease Brit med Bull, 13: 39, 1957.


CHAPTER XX Barnett (1956) described his experience over 5 years with the treatment of 67 severe hypertensives with ganglion blocking

Our general impression is that very high dose patients on oral pentolinium generally benefit by transfer to mecamylamine but the average patient has more parasympathetic side effects with mecamylamine. So far we have not encountered any delayed toxic reactions. Schroeder (1956), however, reports that in patients with malignant hypertension and poor renal function mecamylamine in high doses has produced a most distressing disturbance characterized by generalized severe coarse or flapping tremor (disappearing with sleep) and intense anxiety. Recovery has taken 1 to 3 weeks.

We found the combination of mecamylamine with Rauwolfia alkaloids was helpful in maintaining a smooth control over the blood pressure with decrease of side effects.

Additional information and reviews based on longer experience are available on some of the older drugs. Bromage (1956) found an increase in the vital capacity after reducing the blood pressure by various means: pentamethonium, epidural block and subarachnoid block. The effects were more striking in patients with initial dyspnoea or orthopnoea. In such patients the increase was usually over 200 ml. and often over 400 ml. Presumably the effect was due mainly to decrease in pulmonary congestion.

Abrahams and Wilson (1957) and Wilson and Abrahams (1957) find that hypotensive therapy usually caused no deterioration of renal function in chronic type 1 nephritis, pyelonephritis and malignant hypertension if the initial creatinine clearance was over 50 per cent and the blood urea level below 60 mg. per 100 ml. Renal failure progressed when the initial creatinine clearance was below 30 per cent and the blood urea above 70 mg. per 100 ml.

Smith (1956) reported an acute hallucinatory episode of some days duration in a female patient with severe hypertension which followed blood pressure reduction with hexamethonium. She recovered fully some days after stopping hexamethonium and remarked, "I must have been daft but it did seem real."

Park and Cockersole (1956) described another case of so-called "hexamethonium lung", characterised by "solid oedema" and widespread fine fibrosis.

Davignon et al. (1956) consider that it is impracticable to have patients sleeping at an angle of 45 degrees, but the great majority of our patients, numbering about 400, do so. In over six years we have not encountered the so-called hexamethonium lung in treated cases. We think that the tilted posture at night may have prevented the development of this condition, and is an important feature of a therapeutic régime in that, with an adequate night dose of a ganglion blocking drug and the sitting posture, there is no loss of control over the blood pressure level during sleep.

Slosberg (1956) has described the use of hypotensive therapy in cases

CHAPTER XXI While the literature of late 1956 and early 1957 contains examples of [illegible] as an inefficient stop-gap, [illegible] opinion is now widespread th[illegible], the outlook is greatly improved; and indeed that *treatment by hypotensive* drugs should be undertaken in most severely hypertensive patients.

Yet scrutiny of many published papers convinces me that the results obtained could be improved without adding to the means at our disposal. All too frequently in our own clinic I find that some inadequacy in the patient's understanding of instructions or lack of alertness on our part has been responsible for return of symptoms or even a fatal complication. Ronnov-Jessen (1956), Hood (1956) and Barnett (1956), whose results nearly correspond with ours, hold the view that results depend on the detail of supervision and patient instruction.

Hood (1956) has published a comparison of the results obtained by adequate, as contrasted with inadequate, techniques of administration. Survivals in malignant hypertension patients were very much better in the patients on adequate treatment.

The results from our clinic (Smirk, 1956) show a considerable reduction in mortality with improved control over blood pressure levels following the use of pentolinium and pentolinium in combination with a Rauwolfia alkaloid. Thus, the mortality in grade 3 cases fell from 28 per cent on hexamethonium to 9.9 per cent per annum on the pentolinium combination, and in grade 2 cases from 12 to 2.8 per cent per annum. The results in grades 3 and 2 represent together 701 life years of experience with the treatments.

In malignant hypertension cases in 1956 we had 25 survivors out of 44 patients and 8 had lasted between 5 and 6 years. At 4 years we had 56 per cent survivors A recent survey (April, 1957) shows 43 per cent survivors among the malignant hypertension patients who started treatment between 5 and 7 years ago.

Beaven and Murphy (1956) have reported a *high incidence* of death from dissecting aneurysm in patients treated with methonium drugs. I know of one case proved at autopsy in which dissection occurred in the first few weeks of treatment. This is an incidence of 1 or 2 cases in a series of nearly 500 patients

BARNETT, A J Treatment of severe arterial hypertension: results from long-term use of methonium compounds with and without the addition of reserpine Aust Ann Med, 5. 274, 1956

BEAVEN, D W, and MURPHY, E A Dissecting aneurysm during methonium therapy a report of nine cases treated for *hypertension*. Brit. med. J., 1: 77, 1956

HOOD, B Five and a half years' experience of combinations of hypotensive drugs main present difficulties Hypotensive drugs: Proceedings of a symposium on hypotensive drugs and the control of vascular tone in hyperten-

drugs. There were 21 deaths usually due to a cerebral vascular accident. Twenty-three of 32 patients with malignant hypertension survived for more than 1 year. Symptomatic relief was: headache (42 out of 48), impaired vision (8 out of 40), exertional dyspnoea (21 out of 27), paroxysmal dyspnoea (14 out of 14), angina (5 out of 6), minor cerebral disturbances (9 out of 11), loss of energy (10 out of 21) and nervous tension (5 out of 13).

Barnett et al. (1956) studied the effect of reserpine and of reserpine with hydralazine in benign hypertension. They found side effects troublesome and felt that treatment with these drugs alone was not usually helpful in such patients. Douthwaite (1956), however, thought that the combination of reserpine and hydralazine should be tried first in patients with severe benign hypertension and if this fails reserpine and pentolinium should be tried.

Fitzgerald (1956) has investigated the use of Methergine as an oxytocic and finds that, for hypertension cases in pregnancy, it has the advantage that it does not raise the blood pressure.

Perry and Schroeder, (1956) using a combination of a ganglion blocking drug and hydralazine in 82 patients with malignant hypertension found that of 46 with a non protein nitrogen between 30 and 60 mg. per 100 ml. 27 are alive and working after an average of 21.8 months. Only one of 20 patients with more severe initial azotaemia survived.

Goddard et al. (1955) have abandoned hydralazine because of the side effects and prefer pentolinium to hexamethonium. They usually start with reserpine, 0.25 mg. twice daily; if this proves ineffective they add protoveratrine (A and B), 0.5 mg. thrice daily after meals, increased by 0.25 mg. increments until lowering of the blood pressure or nausea occurs. If the blood pressure remains elevated the addition of pentolinium is considered.

BARNETT, A. J. Treatment of severe arterial hypterension: results from long-term use of methonium compounds with and without the addition of reserpine. Aust. Ann Med , 5: 274, 1956

BARNETT, A J., DOWN, M and HAMILTON, M A trial of treatment of benign hypertension with reserpine and hydralazine Alfred Hosp clin. Rep. (Melbourne), 6: 67, 1956

DOUTHWAITE, A H The use of drugs in hypertension Acta med. scand , 312: 153, 1956

FITZGERALD, W J. Methergine, a study of its effect on blood pressure Obstet. gynec Surv , 8: 167, 1956

GODDARD, C. R , PAULUS, E. W , and BOZEK, T T Hypertension for the general practitioner. J. Iowa St. med Soc , 45: 224, 1955.

PERRY, H. M. Jr , and SCHROEDER, H A Studies on the control of hypertension. VII effects of ganglionic blockade combined with hydralazine on the malignant stage complicated by renal azotemia Circulation (N.Y ), 14: 105, 1956.

# INDEX



VV

sion, held in London, April 5th and 6th, 1956 at the Wellcome Foundation. Pergamon Press, Lond., p. 135, 1956.

Rönnov-Jessen, V. Preliminary results of drug treatment in long-term management of patients with hypertension. Acta med. scand, suppl. 312: 157, 1956.

Smirk, F. H. Principles and details of hypotensive therapy. Hypotensive drugs: Proceedings of a symposium on hypotensive drugs and the control of vascular tone in hypertension, held in London, April 5th and 6th, 1956 at the Wellcome Foundation. Pergamon Press, Lond., p. 109, 1956.